AD NUMBER

ADB272667

NEW LIMITATION CHANGE

TO

Approved for public release, distribution unlimited

FROM

Distribution authorized to U.S. Gov't. agencies only; Proprietary Info.; Oct 2001. Other requests shall be referred to U.S. Army Medical Research and Materiel Command, 504 Scott St., Ft. Detrick, MD 21702-5012.

AUTHORITY

USAMRMC ltr, 18 Apr 2003

AD_____

Award Number: DAMD17-00-2-0065

TITLE: Non-Invasive Ultrasonic Diagnosing and Monitoring of Intracranial Pressure/Volume

PRINCIPAL INVESTIGATOR: Aloyzas Petrikas, Ph.D.

CONTRACTING ORGANIZATION: Vitta Corporation
Bethel, Connecticut 06801

REPORT DATE: October 2001

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 074-0188

1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	October 2001	Annual (1 Oct 00 - 30 Sep 01)

4. TITLE AND SUBTITLE
Non-Invasive Ultrasonic Diagnosing and Monitoring of Intracranial Pressure/Volume

5. FUNDING NUMBERS
DAMD17-00-2-0065

6. AUTHOR(S)
Aloyzas Petrikas, Ph.D.

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
Vitta Corporation
Bethel, Connecticut 06801

E-mail: apetrikas@vitta.com

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSORING / MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES
Report contains color

12a. DISTRIBUTION / AVAILABILITY STATEMENT
Distribution authorized to U.S. Government agencies only (proprietary information, Oct 01). Other requests for this document shall be referred to U.S. Army Medical Research and Materiel Command, 504 Scott Street, Fort Detrick, Maryland 21702-5012.

12b. DISTRIBUTION CODE

13. ABSTRACT ***(Maximum 200 Words)***

Objectives are to verify the innovative concepts of non-invasive intracranial pressure (ICP) absolute value measurement and non-invasive cerebrovascular autoregulation continuous monitoring, to prove the design concepts and to perform the limited clinical trials of the new prototype devices. These devices were designed and successfully tested.

Slow intracranial and ABP wave correlation methodology was used for cerebrovascular autoregulation monitoring. Prototype of non-invasive slow wave monitor has been used together with invasive ICP and ABP slow wave monitors in the ICU. Patients with traumatic brain injuries were monitored. Also a prototype of ultrasonographic absolute ICP meter was applied for periodic non-invasive ICP measurements on the same patients following Clinical Research Protocol No.99124006, AIBS No.990135, HSSRB log No.A-9676.

Continuous monitoring of the correlation factor between invasively recorded ICP and ABP slow waves was performed simultaneously with non-invasive monitoring of correlation factor between volumetric parenchymal blood volume slow waves and ABP slow waves. It has been shown experimentally that non-invasive autoregulation monitoring reflects the same autoregulation state dynamic as invasive autoregulation monitoring. The preliminary results of non-invasive ICP measurement method clinical assessment show that this is only method for non-invasive ICP measurement without the problem of individual calibration of system "patient – non-invasive ICP meter".

14. Subject Terms (keywords previously assigned to proposal abstract or terms which apply to this award)
Non-invasive physiological monitoring, intracranial pressure, cerebrovascular autoregulation, traumatic brain injury

15. NUMBER OF PAGES
72

16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Unlimited

NOTICE

USING GOVERNMENT DRAWINGS, SPECIFICATIONS, OR OTHER DATA INCLUDED IN THIS DOCUMENT FOR ANY PURPOSE OTHER THAN GOVERNMENT PROCUREMENT DOES NOT IN ANY WAY OBLIGATE THE U.S. GOVERNMENT. THE FACT THAT THE GOVERNMENT FORMULATED OR SUPPLIED THE DRAWINGS, SPECIFICATIONS, OR OTHER DATA DOES NOT LICENSE THE HOLDER OR ANY OTHER PERSON OR CORPORATION; OR CONVEY ANY RIGHTS OR PERMISSION TO MANUFACTURE, USE, OR SELL ANY PATENTED INVENTION THAT MAY RELATE TO THEM.

LIMITED RIGHTS LEGEND

Award Number: DAMD17-00-2-0065
Organization: Vitta Corporation

Those portions of the technical data contained in this report marked as limited rights data shall not, without the written permission of the above contractor, be (a) released or disclosed outside the government, (b) used by the Government for manufacture or, in the case of computer software documentation, for preparing the same or similar computer software, or (c) used by a party other than the Government, except that the Government may release or disclose technical data to persons outside the Government, or permit the use of technical data by such persons, if (i) such release, disclosure, or use is necessary for emergency repair or overhaul or (ii) is a release or disclosure of technical data (other than detailed manufacturing or process data) to, or use of such data by, a foreign government that is in the interest of the Government and is required for evaluational or informational purposes, provided in either case that such release, disclosure or use is made subject to a prohibition that the person to whom the data is released or disclosed may not further use, release or disclose such data, and the contractor or subcontractor or subcontractor asserting the restriction is notified of such release, disclosure or use. This legend, together with the indications of the portions of this data which are subject to such limitations, shall be included on any reproduction hereof which includes any part of the portions subject to such limitations.

THIS TECHNICAL REPORT HAS BEEN REVIEWED AND IS APPROVED FOR PUBLICATION.

Valerie Fitts for 11/16/01
LTC Geoff Ling

_____

_____ _____

TABLE OF CONTENTS

INTRODUCTION

The key objectives of the study are to verify the innovative concepts for non-invasive intracranial pressure (ICP) absolute value measurement and for non-invasive cerebrovascular autoregulation continuous monitoring, to prove the design concepts and to perform the limited clinical trials of the new prototype devices. These prototype devices have been designed and successfully preliminarily tested during the first year of this two-year study.

A slow ICP and ABP wave correlation methodology can be used for cerebrovascular autoregulation monitoring. A prototype of a non-invasive human brain intraparenchymal blood volume slow wave monitor has been used together with invasive ICP and ABP slow wave monitors in the ICU. Patients with traumatic brain injuries were monitored simultaneously with these invasive and non-invasive monitors. Also a prototype of ultrasonographic absolute ICP meter was applied for periodic non-invasive ICP measurements on the same patients following Clinical Research Protocol No.99124006, AIBS No.990135, HSSRB log No.A-9676.

Continuous monitoring of the cross-correlation factor between invasively recorded ICP and ABP slow waves was performed simultaneously with non-invasive monitoring of cross-correlation factor between volumetric intraparenchymal blood volume slow waves and ABP slow waves. A high cross-correlation has been shown between non-invasively and invasively measured slow intracranial B waves. Also it has been shown experimentally that non-invasive autoregulation monitoring reflects the same autoregulation state dynamic as invasive autoregulation monitoring in the cases of impaired or intact cerebrovascular autoregulation. The preliminary results of clinical assessment of non-invasive ICP measurement method show that this is the only method for non-invasive ICP measurement without the problem of individual calibration of the system "patient – non-invasive ICP meter".

BODY

1.0. NON-INVASIVE ICP MEASUREMENT THROUGH THE HUMAN EYE

1.1. NON-INVASIVE ABSOLUTE ICP VALUE MEASUREMENT. STATE OF THE ART

Head injury has devastating economic and social consequences both for the victim and for the society that supports the victim. The World Health Organization estimate that by the year 2010, one in ten families will have a family member with a head injury. Since the head injury is more prevalent in the young and the associated disability does not significantly reduce life expectancy, the result is that the social and economic costs incurred by health and welfare organizations are long term and substantial [1].

Direct measurement of intracranial pressure remains the mainstay of detecting brain swelling after the head injury before the pressure rises to the levels damaging the brain function. At present, the measurement techniques are invasive and require either the placement of a catheter-tip strain gauge device into the brain tissue directly or a fluid filled catheter placed into the cerebral spinal fluid space within the brain. The placement of these catheters damages the brain tissue through which they are placed and entails the risk of causing intracerebral bleeding if the blood vessels are damaged during the placement of the catheter. Due to these risks, intracranial pressure is usually monitored only in the severely head injured patients and only if there is clinical or CT or MRI - imaging evidence of the brain at risk of the raised pressure.

As a consequence, the actual incidence of the raised intracranial pressure (ICP) in the less severely head injured population is not well known. Certainly, there is a significant morbidity associated with both moderate and minor head injury but to what degree that damage is due to the raised ICP or is it potentially treatable is unknown. Is it found that there is evidence that a significant proportion of patients for whom the computer tomography (CT) or magnetic resonance imaging (MRI) scan do not show the evidence of the raised pressure, subsequently go on to develop episodes of the raised intracranial pressure. To define the clinical significance of the raised ICP in these patient groups, the non-invasive ICP monitoring technology is needed.

The ideas of the measurement of ICP non-invasively have been appearing since 1980. There are many patents [2,3,6-19], the authors of which have attempted to find the objects or physiological characteristics of cerebrospinal system that would be related to the ICP and to monitor them non-invasively (Table 1, Fig.1).

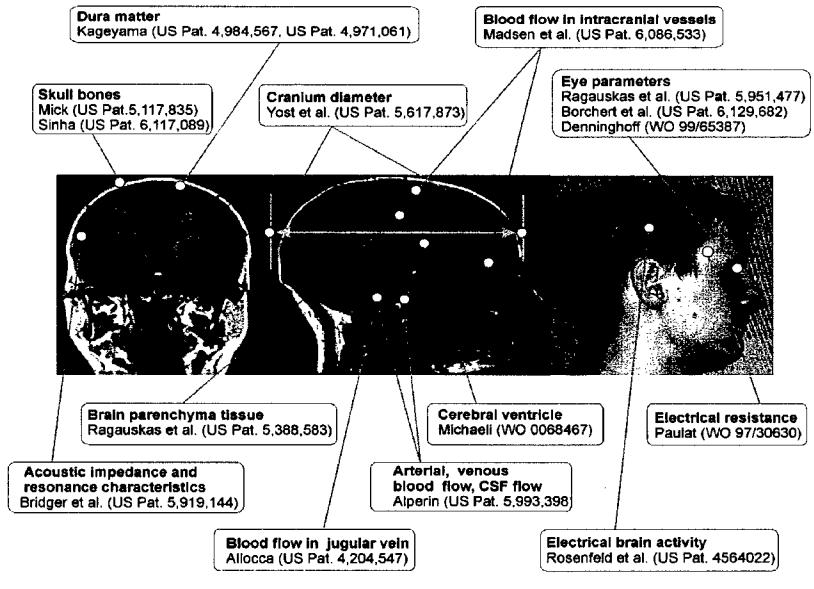


Fig. 1 Different methodologies for non-invasive ICP monitoring

Table 1. **Patents of non-invasive ICP measurement methods.**

Author and patent number,	Year	Object or characteristic related to ICP	Method
Allocca [6] US Pat. 4,204,547	1980	Blood flow in a jugular vein	Occlusion of blood flow in a jugular vein and the electromagnetic measurement of the change of blood flow within the jugular vein upstream of the occlusion
Rosenfeld et al. [7] US Pat. 4564022	1986	Electrical brain activity	Measurement of the changes of electrical brain activity after the light stimulus into the eyes
Kageyama [8] US Pat. 4,971,061	1990	Dura matter thickness	Amplitude measurement of ultrasound interference echoes reflected from dura matter
Kageyama [9] US Pat. 4,984,567	1991	Dura matter thickness	Cepstrum analysis of ultrasound interference echoes reflected from dura matter
Mick [10] US Pat. 5,117,835	1992	Sound attenuation in skull bones	Measurement of ultrasound attenuation in skull bones and signal spectrum analysis
Ragauskas et al. [2] US Pat. 5,388,583	1995	Acoustic properties of brain parenchyma tissue	Ultrasound pulse transmission through the intracranial media and signal time-of-flight measurement
Yost et al. [11] US Pat. 5,617,873	1997	Cranium diameter	Phase measurement of ultrasound signal reflected from the far side of the skull
Paulat [12] WO 97/30630	1997	Electrical resistance of the skull	Signal waveform analysis
Bridger et al. [13] US Pat. 5,919,144	1999	Acoustic impedance and resonance characteristics of the cranium	Low frequency acoustic signal transmission through the cranium and the application of the spectral analysis for a detected signal
Alperin [14] US Pat. 5,993,398	1999	Arterial and venous blood flow and the cerebrospinal fluid flow	Phase contrast magnetic resonance imaging
Denninghoff [15] WO 99/65387	1999	Eye vessels and intraocular pressure	Simultaneous measurement of the $SrVO_2$ saturation in retinal vessels, intraocular pressure and cardiac cycle
Ragauskas et al. [3] US Pat. 5,951,477	1999	Blood flow in the eye artery	Ultrasonic two depth Doppler blood flow measurement technique
Madsen et al. [16] US Pat. 6,086,533	2000	Blood flow in the intracranial vessels	Ultrasonic Doppler blood flow measurement technique
Borchert et al. [17] US Pat. 6,129,682	2000	Parameters of an optic nerve of the eye	Optical coherence tomography
Sinha [18] US Pat. 6,117,089	2000	Stress level of skull bones	Generating and detecting standing waves in the skull bones and the measurement of phase difference between the transmitted oscillatory signal and the received signal
Michaeli [19] WO 0068467	2000	Third cerebral ventricle	Analysis of echo pulsogram waves

Most of the proposed monitoring technologies are based on the ultrasound application and are capable of monitoring physiological properties such as blood flow in intracranial or intraocular vessels, pulsations of the cerebral ventricles, cranium diameter or acoustic properties of the cranium. However, there are a number of major problems encountered by the authors of these works [6-19] including such issues as:

- which biophysical parameter of a cerebrospinal system is a stable function of intracranial pressure or cerebral perfusion pressure (CPP)?
- is that function linear and sufficiently independent of such main influential factors as arterial blood pressure (ABP) and how it depends on the cerebral blood flow autoregulation?
- how to calibrate non-invasively and individually the system "individual patient – non-invasive ICP or CPP meter"?

All the proposed methods (Table 1), with the exception of our method of absolute ICP measurement through the human eye [3], are indirect and need individual calibration of the system "individual patient – non-invasive ICP meter". In all these cases the dilemma appears – wheather the non-invasive absolute ICP calibration method could be created. Such a method can be used also for the absolute ICP measurement. Thus, any non-invasive indirect ICP meters have no sense.

The general solution of absolute ICP measurement is to invent an absolute ICP non-invasive meter, reliable and accurate enough for clinical practice, without the necessity of individual calibration. The "Vittamed Ltd." method [3] of the measurement through the eye is the only

method which does not need individual calibration because this is a direct method of comparison of absolute ICP with extracranial pressure applied to the tissues surrounding the human eye [4,5,20,21].
Our innovative method [3] includes a means based on the transcranial Doppler multi-depth technique for a non-invasive absolute ICP and external absolute pressure comparison.
The concept of non-invasive ICP absolute value measurement [3] is the following:
- the eye artery is used as a natural "transducer" which has two segments – intracranial and extracranial. The intracranial segment is compressed by ICP. The extracranial segment can be compressed by the controlled external pressure applied to the eye ball surrounding tissues;
- the pressure balance can be achieved when the absolute value of external pressure is equal to the ICP. In the case of balance the blood flow parameters in the intracranial segment and extracranial segment of the eye artery are almost equal independently of the absolute value of arterial blood pressure, hydrodynamic resistance of the eye veins, the pressure inside the eye ball and the initial absolute values of the blood flow parameters in both segments of the eye artery;
- a specially designed two-depth pulse wave transcranial Doppler device could be applied to identify this balance. The absolute value of external pressure reflects the absolute ICP value for this balance.

1.2. PRELIMINARY MULTIDEPTH TCD MEASUREMENTS OF THE EYE ARTERY BLOOD FLOW

In order to study the ultrasonic transducer adjustment procedure for two depth eye artery blood flow measurements the multidepth power M - mode TCD technique was used (Spencer Technologies, Seattle, WA, USA). The purpose of such an examination was to show experimentally the ability to identify:
- the internal carotid artery and the depth of it from the surface of the ultrasonic TCD transducer applied to the eye lid;
- to identify blood flow pulse waves in the intracranial and extracranial segments of the eye artery;
- to identify the depths of extracranial and intracranial segment of the eye artery;
- to identify the depths of "input" and "output" of the optic nerve canal.
The experimental results are shown in Fig. 2 – Fig. 16. All results are presented in two windows of the power M – mode TCD device.
The upper window is a M – mode window where the depth of insonation is shown on the X axis and the time is shown on the Y axis. The signals in the upper window represent the depth – time dependencies on the power of ultrasonic signal reflected from the eye artery blood flowing in different depths from the eye lid surface.
The signals in the lower window represent TCD spectra of the eye artery blood flow pulse waves at the selected depth. The selected depth is marked in the upper window as an yellow line.
Fig. 2 – Fig. 10 show the simultaneous measurements of the eye artery and the internal carotid artery power M – mode signals and also TCD signals measured at the depths from 43 mm to 80 mm. The difference of TCD signals measured at the depth of internal carotid artery (65 ... 80 mm) and TCD signals measured at the depths of intra- and extracranial segments of the eye artery (depths 43 ... 58 mm) are clearly seen.
Fig. 11 – Fig. 14 show the simultaneous measurement of eye artery blood flow in the extracranial segment and intracranial segment. Also the eye artery canal could be identified in the upper windows as an area with a decreased power M – mode signal (Fig. 11) between power M – mode signals from extracranial and intracranial segments of the eye artery.
The conclusions from this preliminary experiment are as follows:

- the power M – mode image of the eye artery blood flow could be helpful for fast spatial adjustment of the ultrasonic TCD transducer for simultaneous TCD measurement of blood flow in the intracranial and extracranial segments of the eye artery;
- the power M – mode image is also useful for the identification of "input" and "output" depths of the optic canal. This kind of identification is useful for optimization of the depths of intracranial and extracranial segments of the eye artery;
- the power M – mode imaging technology could be used as a technology for the guidance of two-depth TCD ultrasonic transducer spatial adjustment for simultaneous two-depth eye artery blood flow measurement. Power M – mode technology could be implemented in the final version of a non-invasive absolute ICP meter as an adjustment mode technique. Our preliminary experience is that for spatial adjustment of ultrasonic TCD transducer five freedom degrees (FD) are needed. A five FD microrobotic technique also could also be created in the future for an automatic adjustment of ultrasonic transducer. The adjustment by the hand takes more than 2 minutes for a highly experienced TCD operator.

That experience was used for the design of optimized two-depth TCD transducer for the absolute ICP measurement application and for the design of special two-depth TCD device prototype for that application.

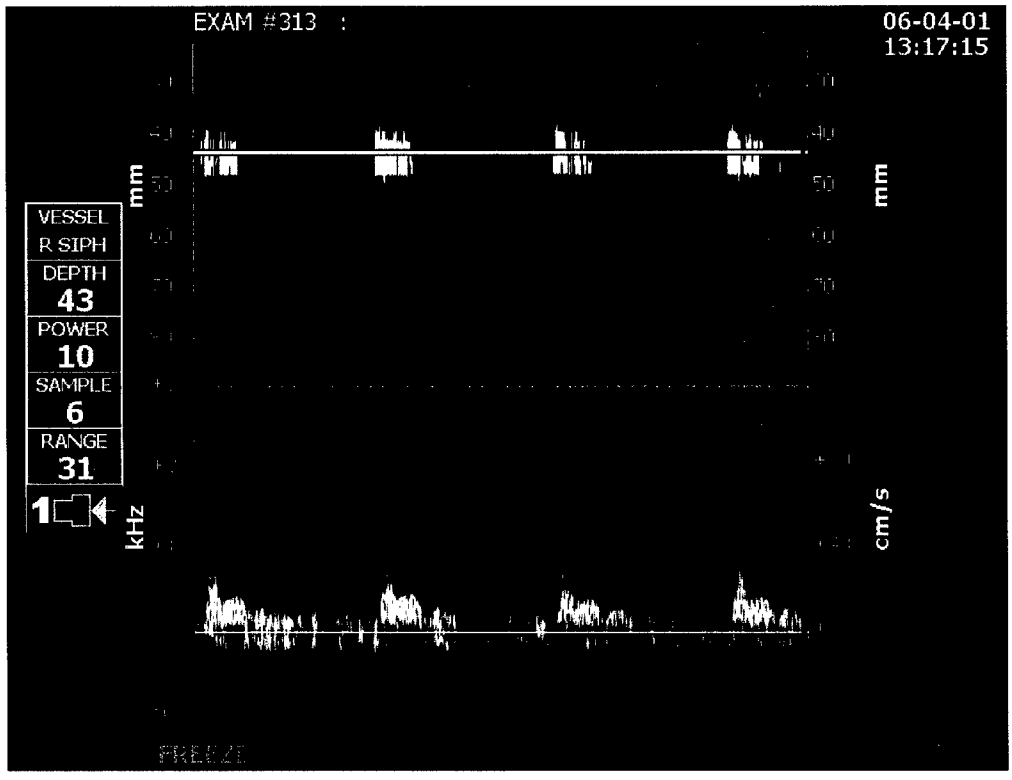


Fig. 2. Fig. 2. Simultaneous measurements of blood flow in the eye artery (depth d = 43 mm) and power M-mode signals of the eye artery and the internal carotid artery

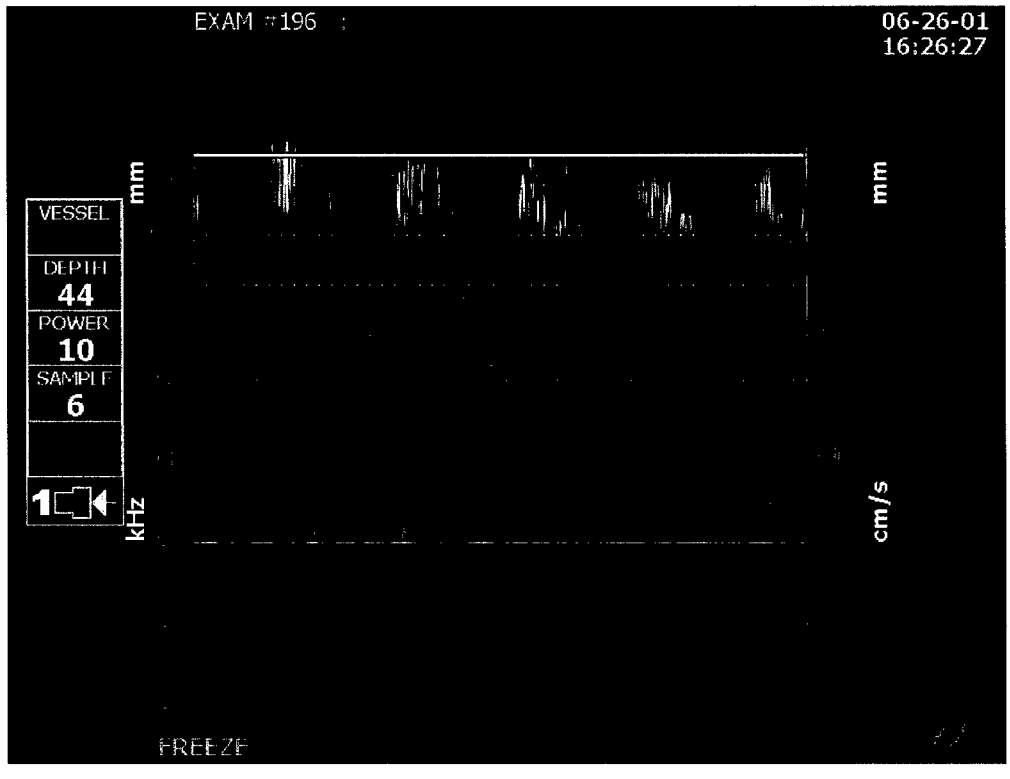


Fig. 3. Simultaneous measurements of blood flow in the eye artery (depth d = 44 mm) and power M-mode signals of the eye artery and the internal carotid artery

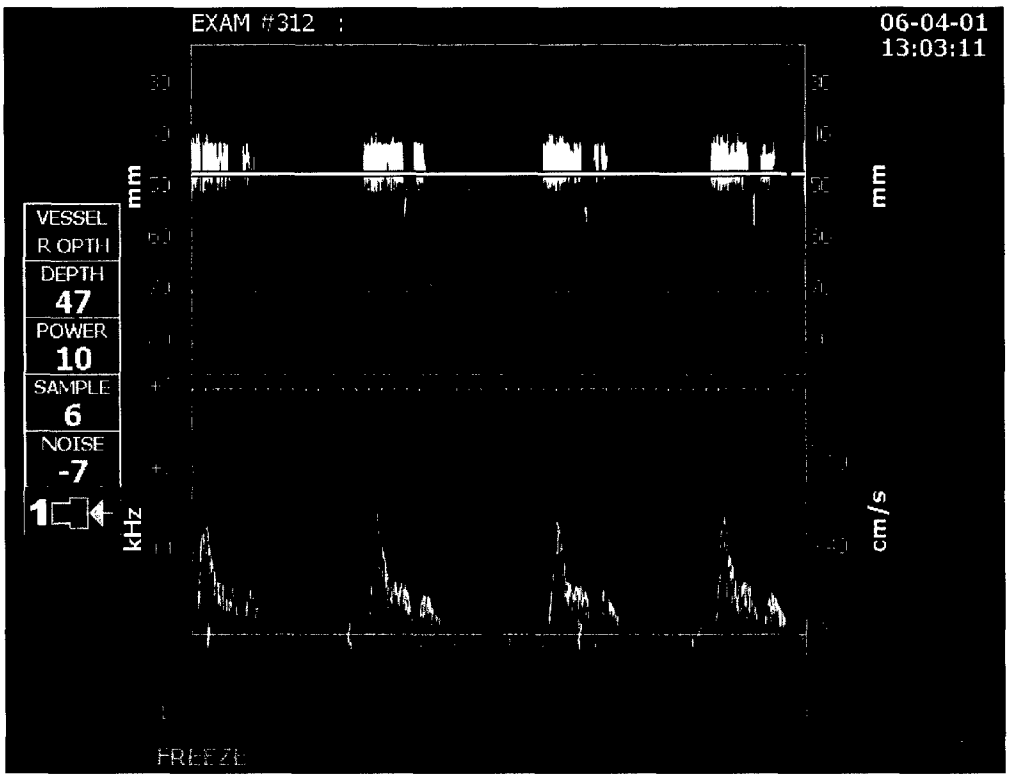


Fig. 4. Simultaneous measurements of blood flow in the eye artery (depth d = 47 mm) and power M-mode signals of the eye artery and the internal carotid artery

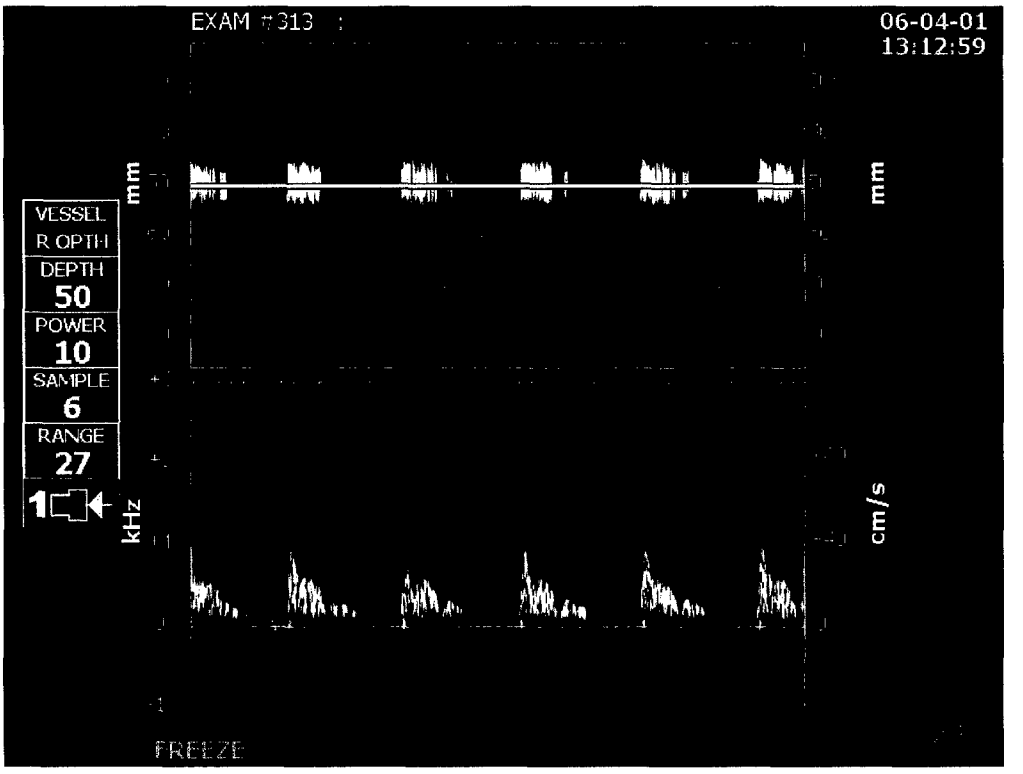


Fig. 5. Simultaneous measurements of blood flow in the eye artery (depth d = 50 mm) and power M-mode signals of the eye artery and the internal carotid artery

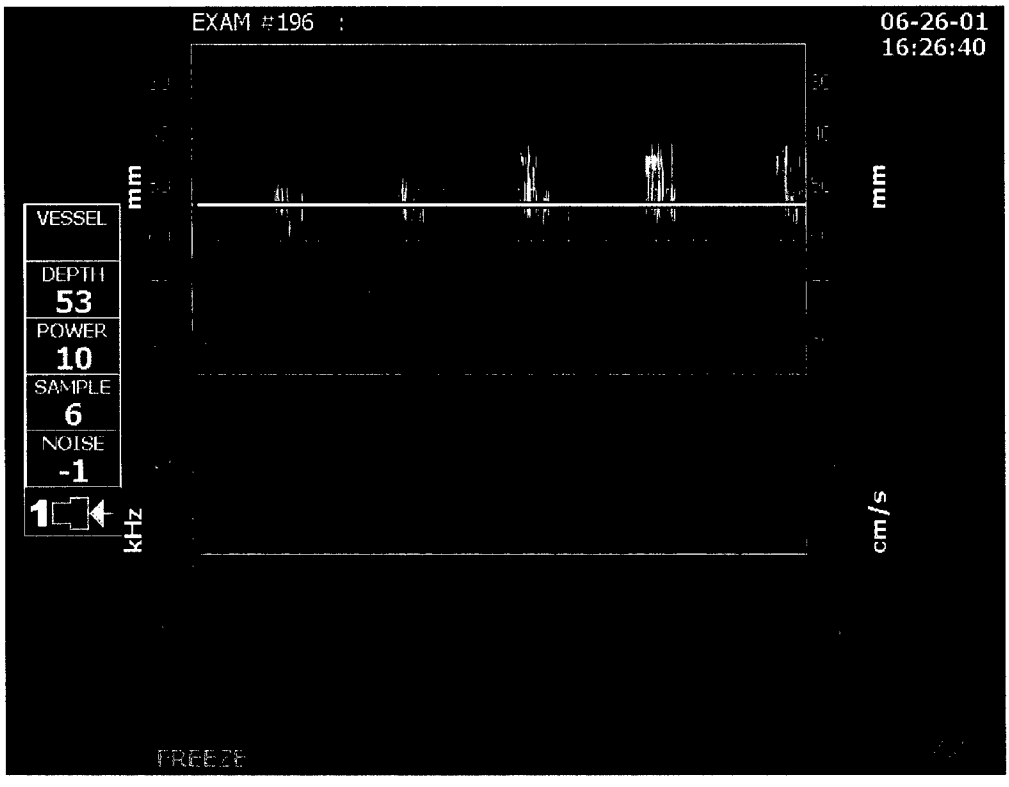


Fig. 6. Simultaneous measurements of blood flow in the eye artery (depth d = 53 mm) and power M-mode signals of the eye artery and the internal carotid artery

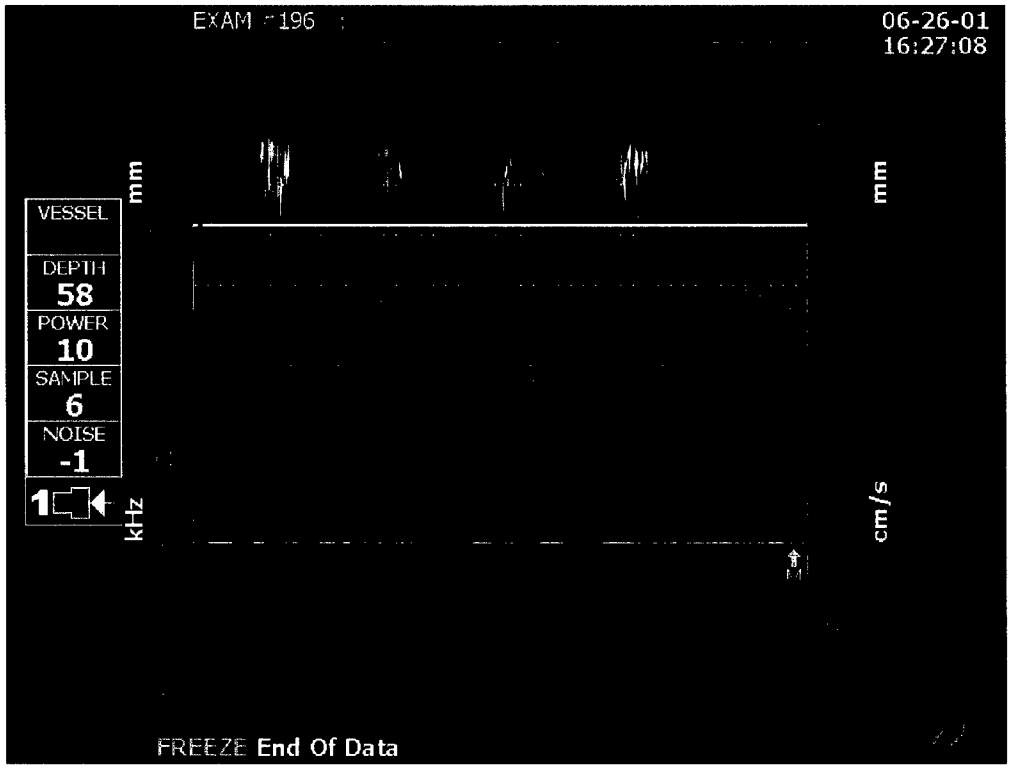


Fig. 7. Simultaneous measurements of blood flow in the eye artery (depth d = 58 mm) and power M-mode signals of the eye artery and the internal carotid artery

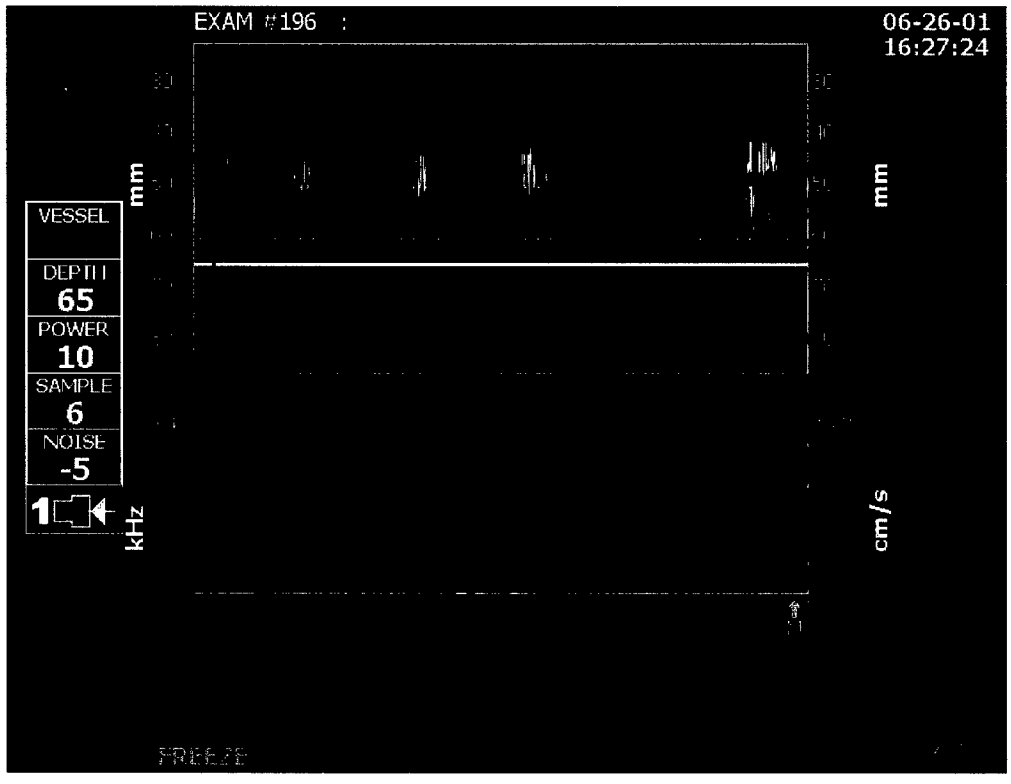


Fig. 8. Simultaneous measurements of blood flow in the eye artery (depth d = 65 mm) and power M-mode signals of the eye artery and the internal carotid artery

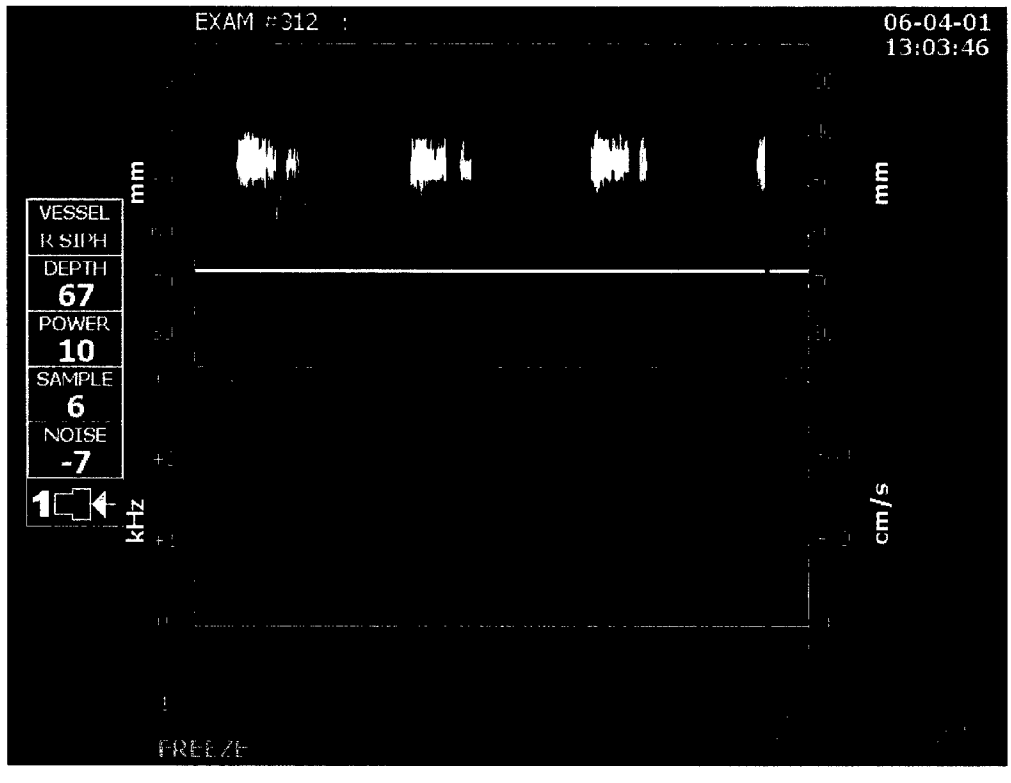


Fig. 9. Simultaneous measurements of blood flow in the eye artery (depth d = 67 mm) and power M-mode signals of the eye artery and the internal carotid artery

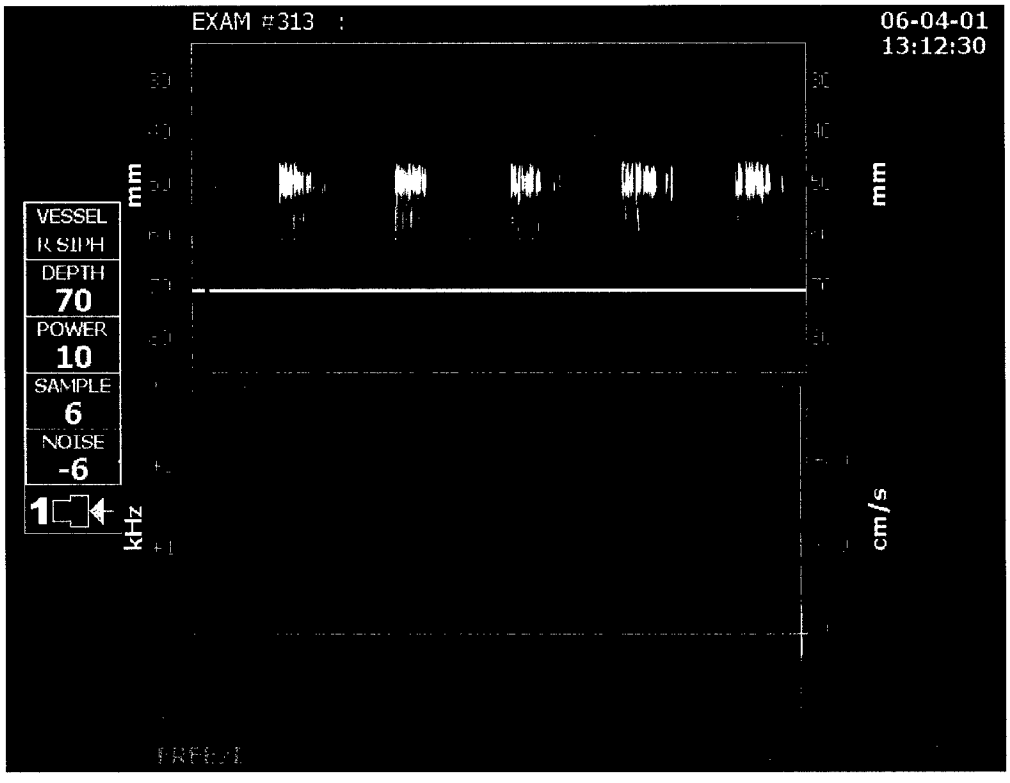


Fig. 10. Simultaneous measurements of blood flow in the eye artery (depth d = 70 mm) and power M-mode signals of the eye artery and the internal carotid artery

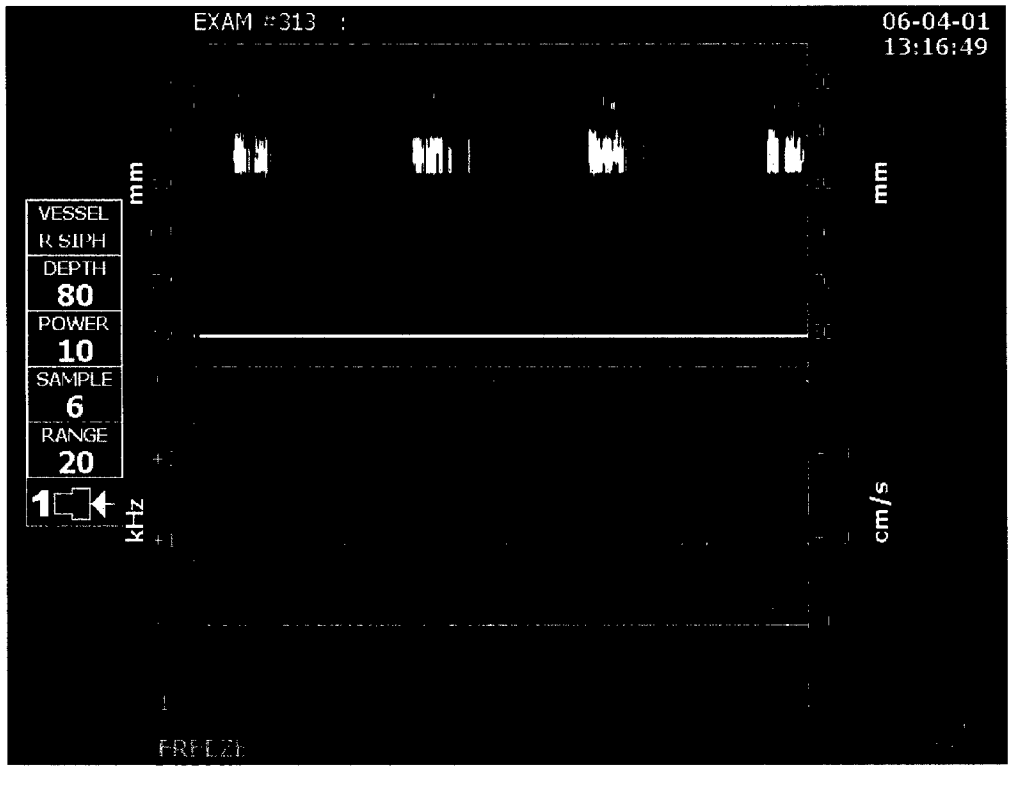


Fig. 11. Simultaneous measurements of blood flow in the eye artery (depth d = 80 mm) and power M-mode signals of the eye artery and the internal carotid artery

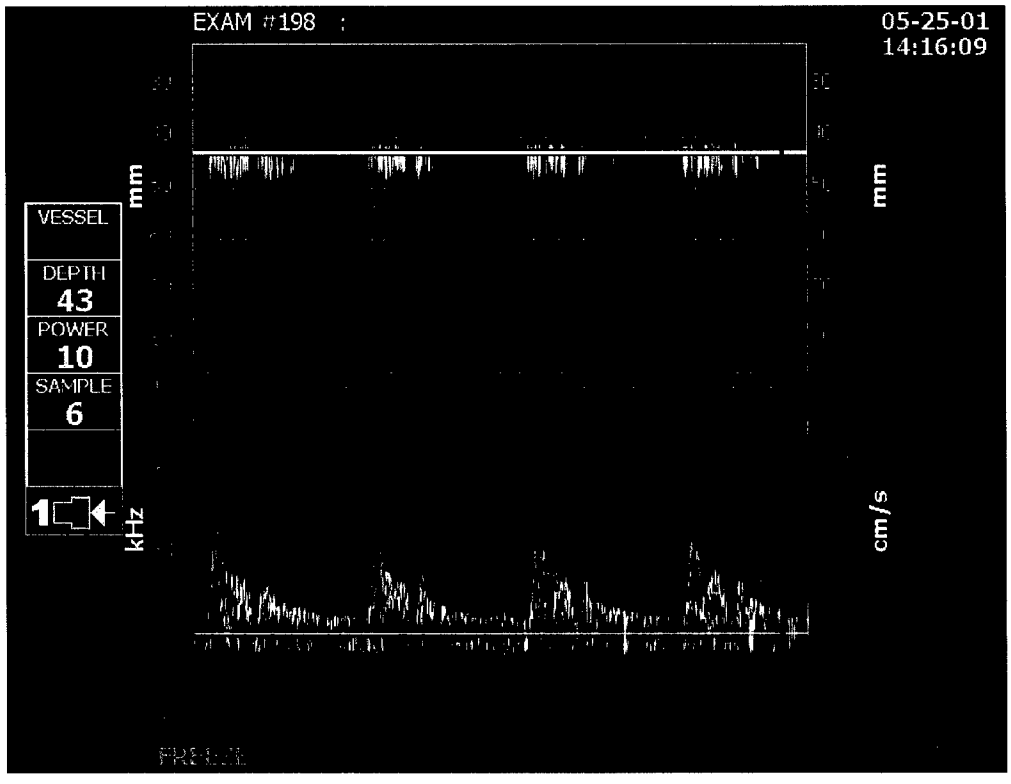


Fig. 12. Simultaneous measurements of blood flow in the eye artery (depth d = 43 mm) and power M-mode signals of the eye artery

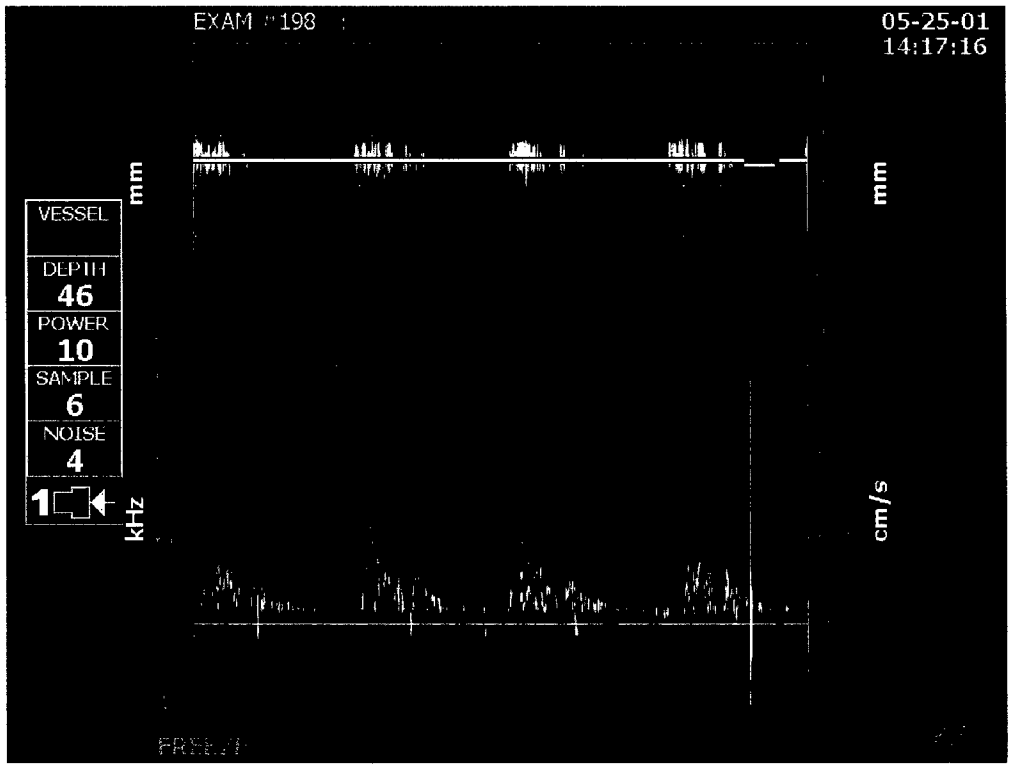


Fig. 13. Simultaneous measurements of blood flow in the eye artery (depth d = 46 mm) and power M-mode signals of the eye artery

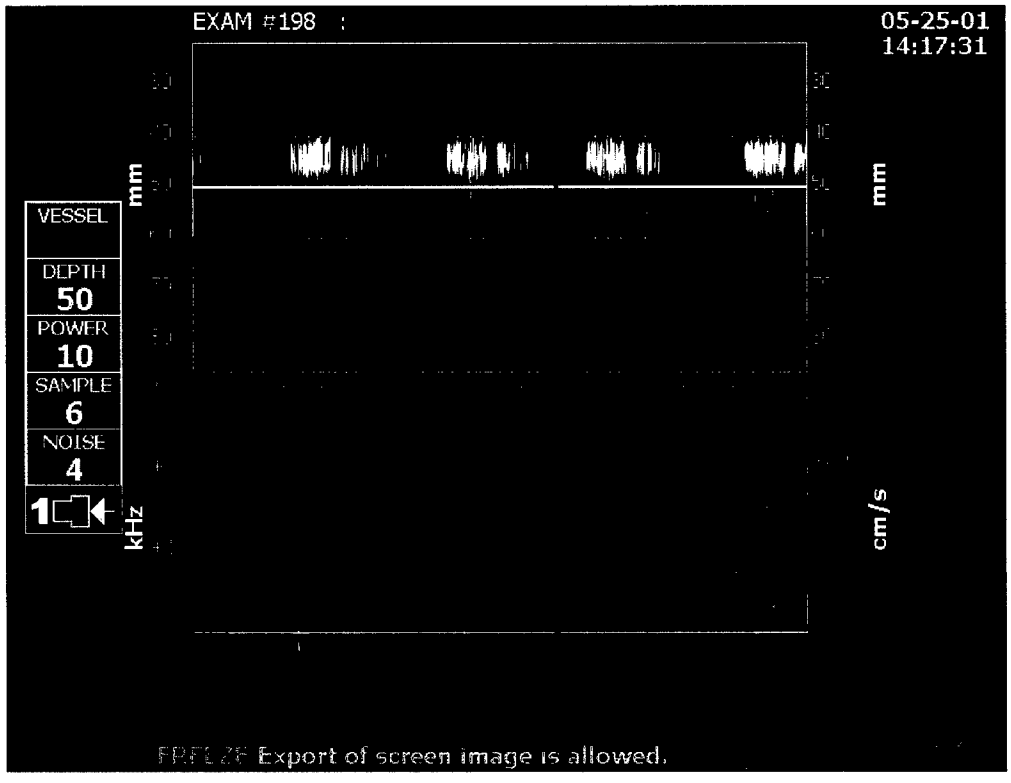


Fig. 14. Simultaneous measurements of blood flow in the eye artery (depth d = 50 mm) and power M-mode signals of the eye artery

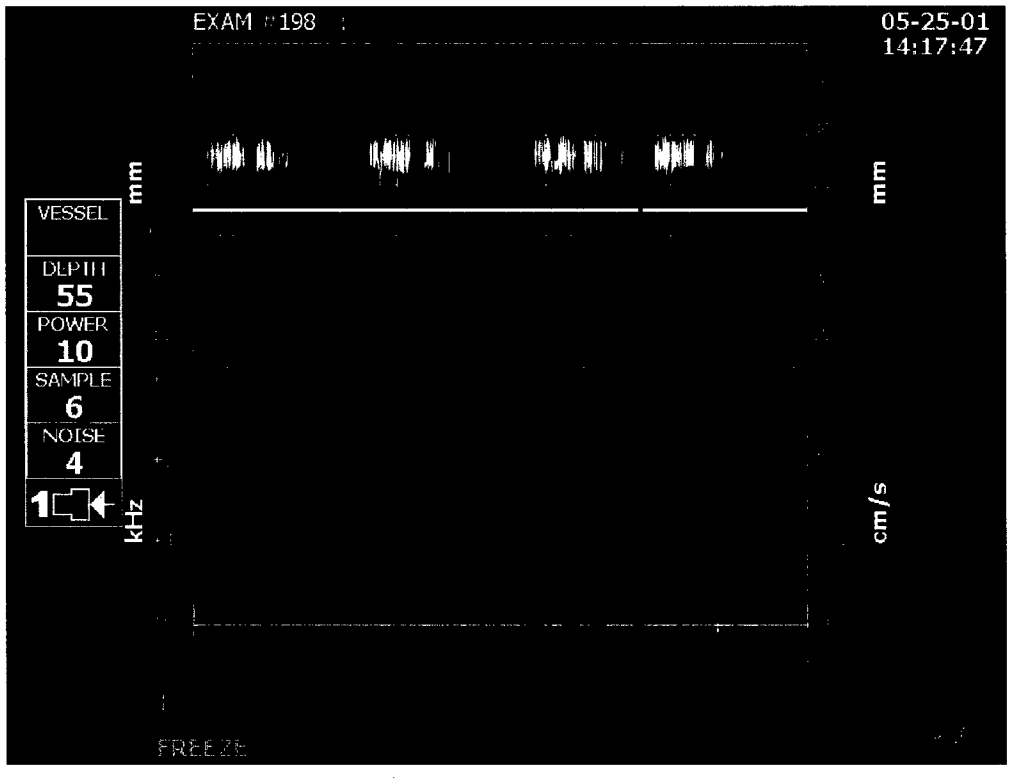


Fig. 15. Simultaneous measurements of blood flow in the eye artery (depth d = 55 mm) and power M-mode signals of the eye artery

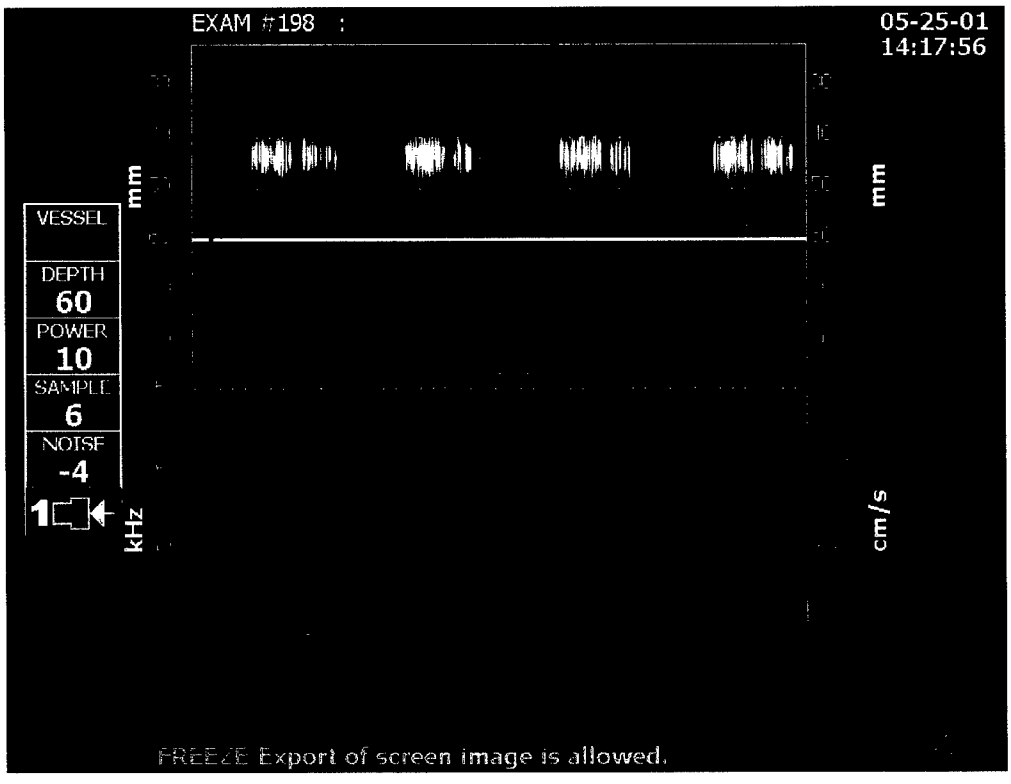


Fig. 16. Simultaneous measurements of blood flow in the eye artery (depth d = 60 mm) and power M-mode signals of the eye artery

1.3. PROTOTYPE OF INNOVATIVE TCD TWO-DEPTH DEVICE FOR EYE ARTERY BLOOD FLOW MEASUREMENT

The portable prototype of a two-depth TCD device (photo 1) consists of an electronic unit, an ultrasonic 2.0 MHz transducer, a pressure chamber, a pump and a mechanical (in this particular version) extracranial pressure meter.

The electronic unit is powered by a lead-acid battery power only when recording from human subjects. The dimensions of the electronic unit are 200x200x130 mm^3. The unit is designed for the possibility to operate with different ultrasonic transducers with central frequencies ranging from 1.0 MHz to 10.0 MHz.

For a recorded data storage, a flash–disk is used. The size of the flash disk is 14 Mbytes but may vary up to 288 Mbytes depending on the option. The device has a serial RS232 interface for the recorded data transfer to the external PC. The device can measure the eye artery blood flow parameters in two depths simultaneously. The minimal depth is 0 mm, the maximal depth is 200 mm. The possible difference in the two depths can range from 3.7 mm to 24 mm. The burst (spatial sampling step) can be from 1.1 mm to 7 mm. The instrument can record blood flow pulse waves at a sampling rate of 100 Hz and transfer the data to PC at the rate of 115200 kBaud.

The maximum output ultrasound power is 82 mW (burst more than 3.1 mm, velocity scale from –200 cm/s to +200 cm/s).

The device can record and display the eye artery blood flow velocity pulse waves in the extracranial and intracranial segments simultaneously. Also, it is possible to display the waves from both depths in the same window for their shape comparison. Raw TCD data can also be used for comparison of blood flow parameters in both depths of the eye artery.

1.4. PROTOTYPE OF TCD ULTRASONIC TRANSDUCER OPTIMIZED FOR INTRACRANIAL AND EXTRACRANIAL EYE ARTERY SEGMENTS INSONATION

A prototype of TCD ultrasonic transducer was developed and manufactured for the eye artery application. Our experimental experience says that only a slight difference in the signal to the noise ratio could be achieved if the central frequency of the ultrasonic signal is increased from 2.0 MHz to 4.0 MHz for that application. Because of that we have decided to use a prototype ultrasonic transducer with the central frequency 2.0 MHz. The optimization of spatial properties of the ultrasonic transducer was based on the knowledge of anatomical depths (from the surface of the eye lid) of "input" and "output" of the optic nerve canal. The length of optic nerve canal is from 9.0 mm to 12.0 mm. The depth of its "input" is about 48...50 mm. Spatial characteristics of ultrasound pressure of the prototype transducer are shown in Fig. 17 - Fig. 19.

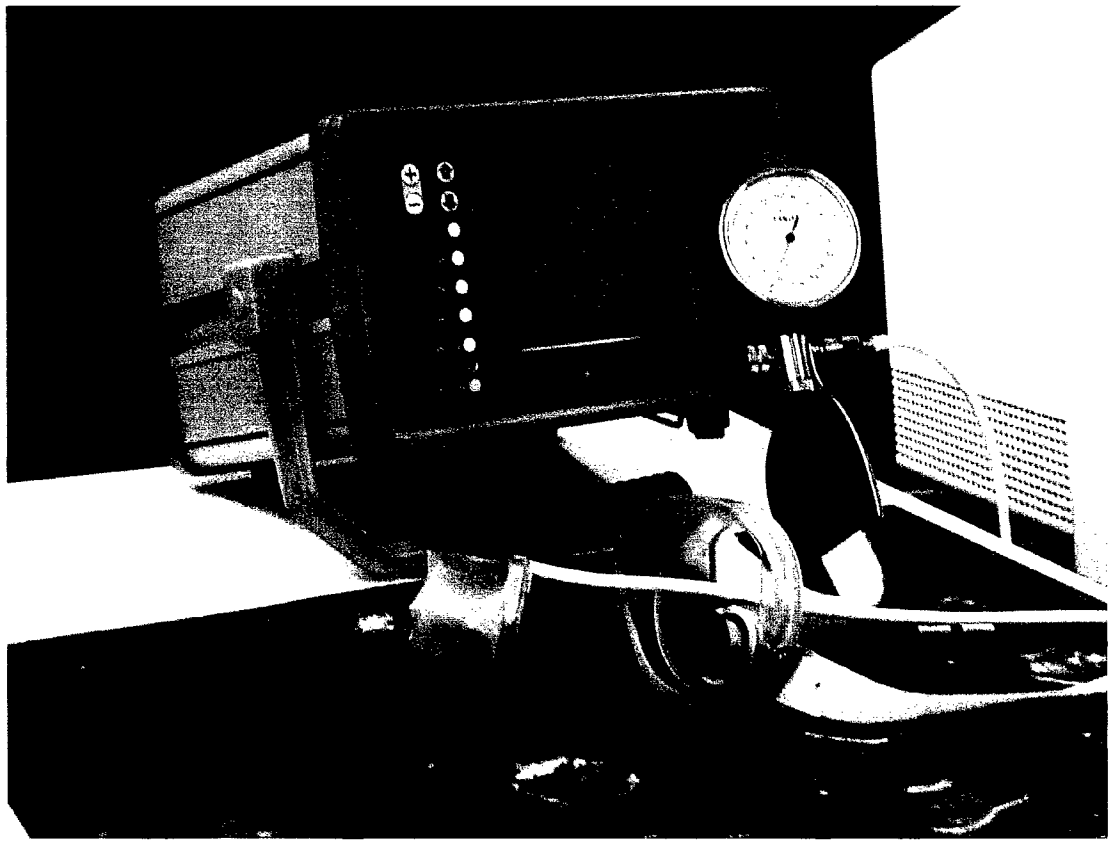


Photo 1. Prototype of a non-invasive Vittamed absolute ICP meter which consists of a two-depth TCD device, a ultrasonic transducer, an extracranial pressure chamber, a pump and a mechanical meter of extracranial pressure

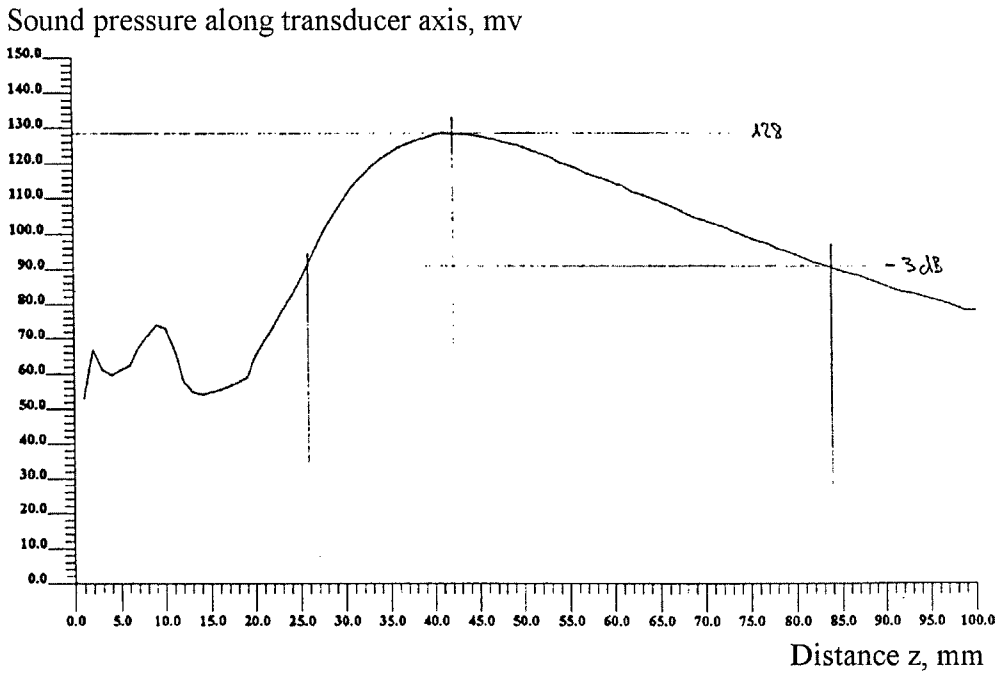


Fig. 17. Sound pressure along ultrasonic field central axis. The maximal pressure is obtained at the distance z = 42 mm. The distance with –3dB level is from z = 26 mm to z = 83 mm.

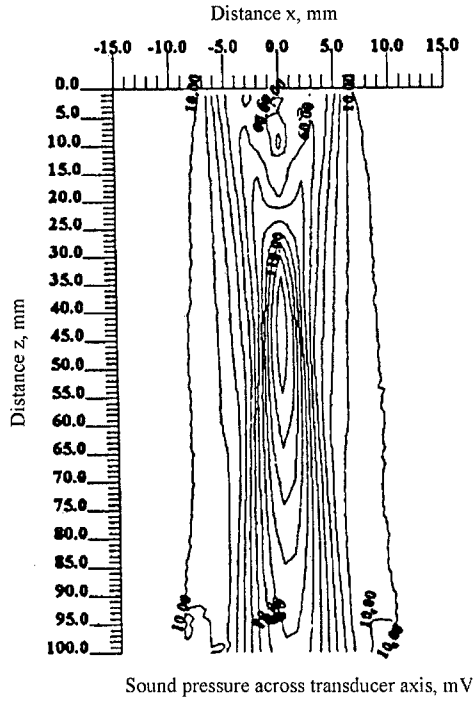


Fig. 18. Sound pressure along and across ultrasonic field

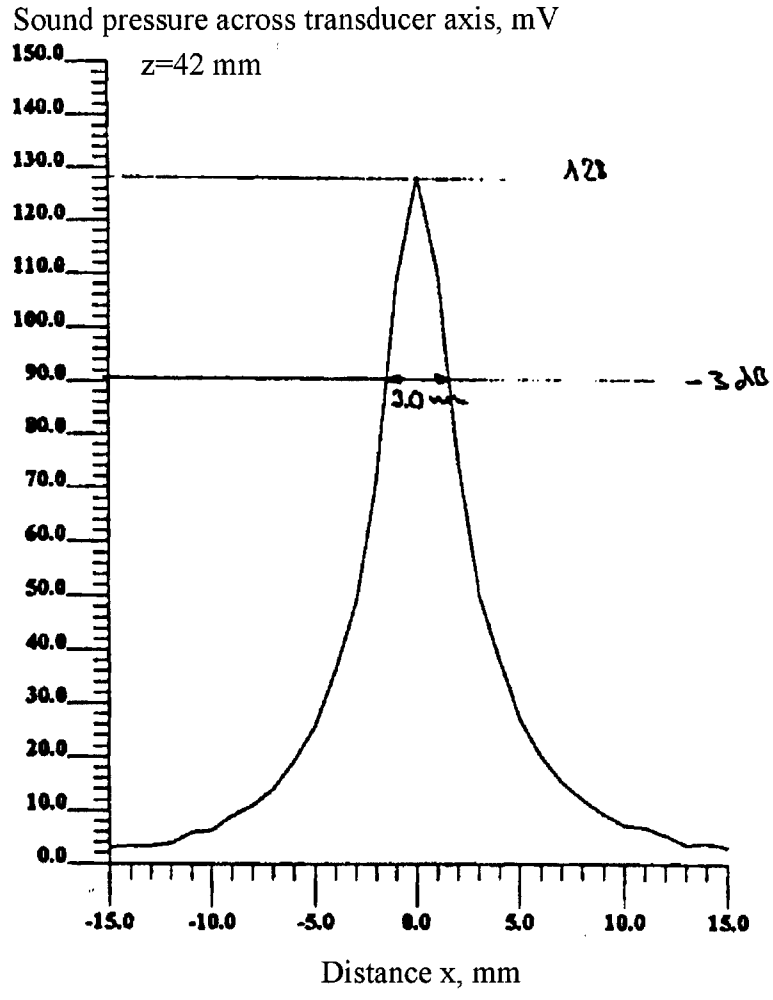


Fig. 19. Sound pressure across ultrasonic field central axis

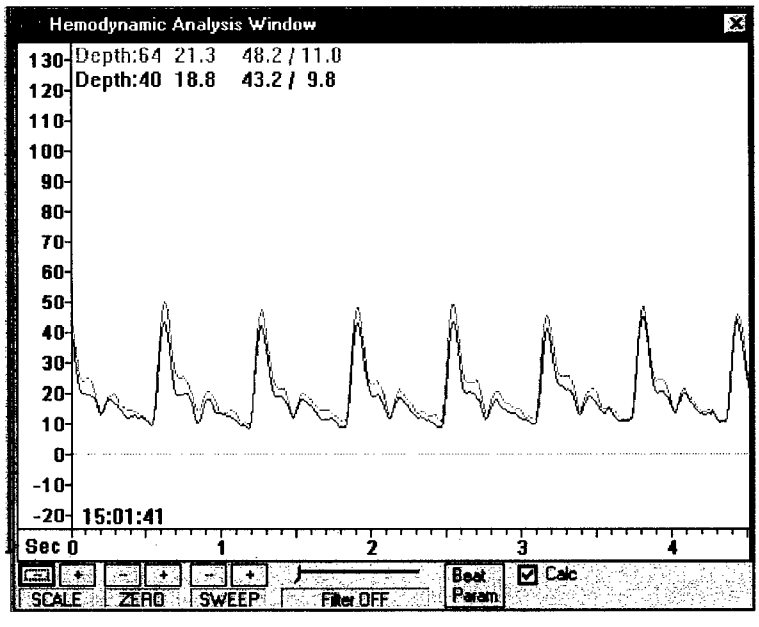


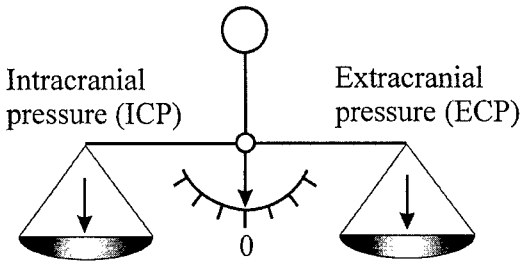
Fig. 20. Virtual panel of the prototype of two-depth TCD device for non-invasive Vittamed absolute ICP meter. Blood flow in the eye artery is registered at the depth d = 64 mm and d = 40 mm simultaneously, when external pressure is Pe = 0 mmHg

1.5. THE RESULTS OF PRELIMINARY CLINICAL TESTING OF THE PROTOTYPE ABSOLUTE ICP METER

The prototype meter was successfully tested in the ICU. Standard pulsatility indexes were applied for preliminary intracranial and extracranial eye artery blood flow balance identification (Fig. 21) under ICU conditions. 15 non-invasive absolute ICP measurements were performed on ICU patients (traumatic brain injuries) simultaneously with invasive ICP measurements following Clinical Research Protocol No. 9912 4006, AIBS No. 990135, HSSRB Log No. A – 9676. The clinical study is continuing and will be completed when 52 invasive and non-invasive monitoring one-hour periods are performed.

NON-INVASIVE ABSOLUTE ICP VALUE MEASUREMENT METHOD

(without the problem of individual calibration of system
"patient - non-invasive ICP meter")



BALANCE OF SCALES: ICP = ECP

THIS IS THE ONLY METHOD TO MEASURE THE ABSOLUTE ICP VALUE WITHOUT AN INDIVIDUAL CALIBRATION PROBLEM

Fig. 21. The "scales" for absolute ICP measurement: the left part of the scales is an intracranial segment of the eye artery, the right part of the "scales" is the extracranial segment of the eye artery, the balance of scales is determined comparing blood flow parameters in intracranial and extracranial segments by two-depth TCD device (ideally the balance of scales is achieved when the difference in both blood flows is equal to zero and when ICP = ECP).

A blood flow Gosling pulsatility index (PI) was used for the balance indication (Fig. 21) because this relative parameter of blood flow is independent of the insonation angle. PI is equal to the ratio of the difference between systolic and diastolic blood flow values to the mean blood flow value.

Anatomically the intracranial and extracranial segments of the eye artery could be spatially orientated at different angles from the acoustic axis of the optimally adjusted ultrasonic transducer. This anatomical factor is eliminated applying Gosling PI for balance indication because PI does not depend on the insonation angle.

The dependencies of PI on extracranial pressure Pe in the extracranial segment (depth d=40 mm) and intracranial segment (d=54 mm) of the eye artery measured in ICU applying a prototype two-depth TCD device are shown in Fig. 22–Fig. 25. This is a typical behavior of the intracranial and extracranial eye artery blood flows. The balance of intracranial PI and

extracranial PI is achieved at Pe value very close to the invasively measured absolute ICP value. It is typical that the systematic error (less than 3 mmHg) of the non-invasive absolute ICP meter is always positive primarily because of the arterial blood pressure gradient between the two depths of the eye artery and also because of the pressure gradient between extracranial pressure applied to the extracranial segment of the eye artery and the measured value of Pe inside the pressure chamber.

In order to evaluate the sensitivity and accuracy of two-depth TCD method for absolute ICP measurement we intend to study the applicability of non-standard blood flow pulsatility indexes for blood flow balance indication in intracranial and extracranial segments of the eye artery. Such pulsatility indexes could be introduced applying real-time FFT analysis of pulsating blood flow waveform and applying the ratio between mean harmonic power of waveform spectrum and mean value of blood flow velocity.

The proposed non-standard balance index was preliminary tested applying computer modeling. This new index is more sensitive for balance indication comparing with Gosling pulsatility index. A new software for automatic balance indication applying a new balance index is under creation. In order to obtain the best possible signal to noise ratio in two-depth TCD measuring channels we intend to perform clinical experiments applying standard ultrasonic echo-contrast agents, e.g., Levovist (Schering, Germany). This experiment and application of non-standard pulsatility index for balance indication will let us to evaluate the minimal obtainable absolute error of non-invasive absolute ICP meter.

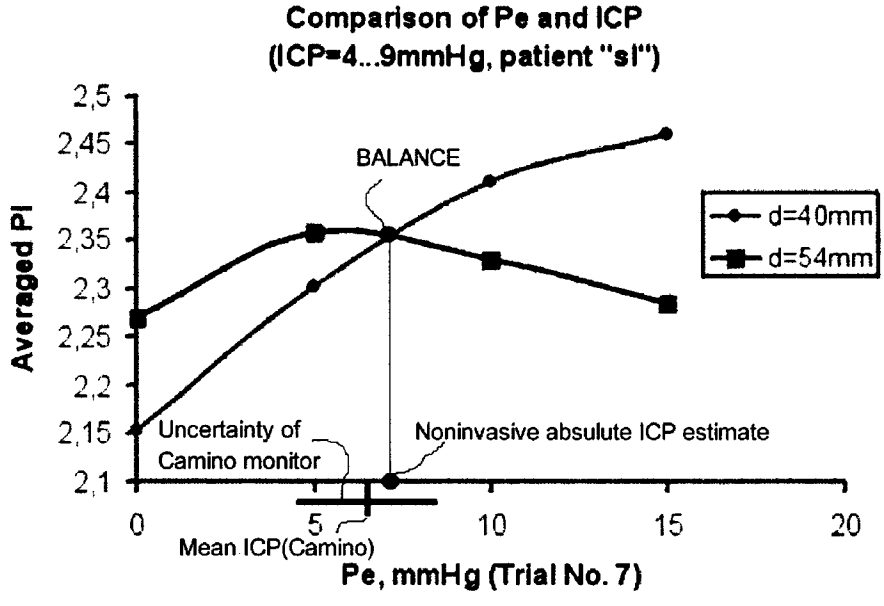


Fig. 22. The dependencies of Gosling pulsatility indexes (PI) on extracranial pressure Pe in the extracranial egment (depth d=40 mm) and intracranial segment (d=54 mm) of the eye artery measured in ICU applying the prototype two-depth TCD device

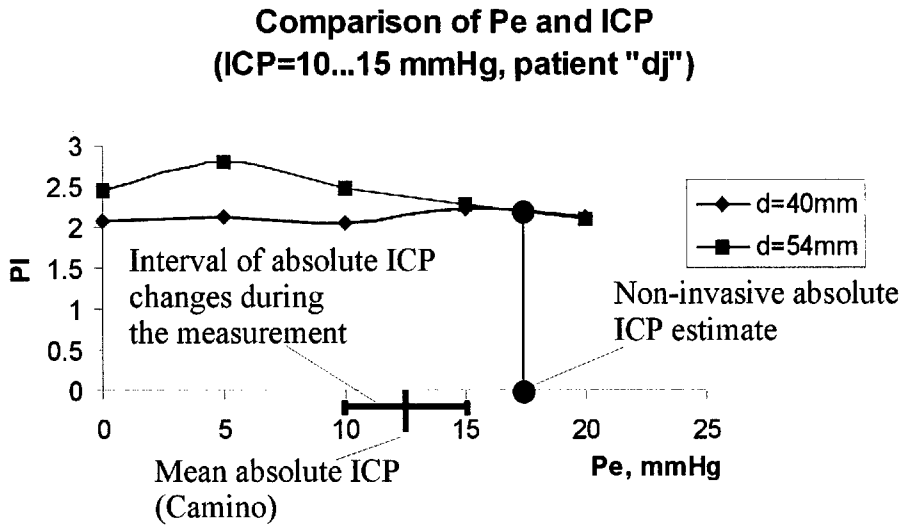


Fig. 23. The dependencies of Gosling pulsatility indexes (PI) on extracranial pressure Pe in the extracranial segment (d=40 mm) and intracranial segment (d=54 mm) of the eye artery measured in ICU applying the prototype two-depth TCD device

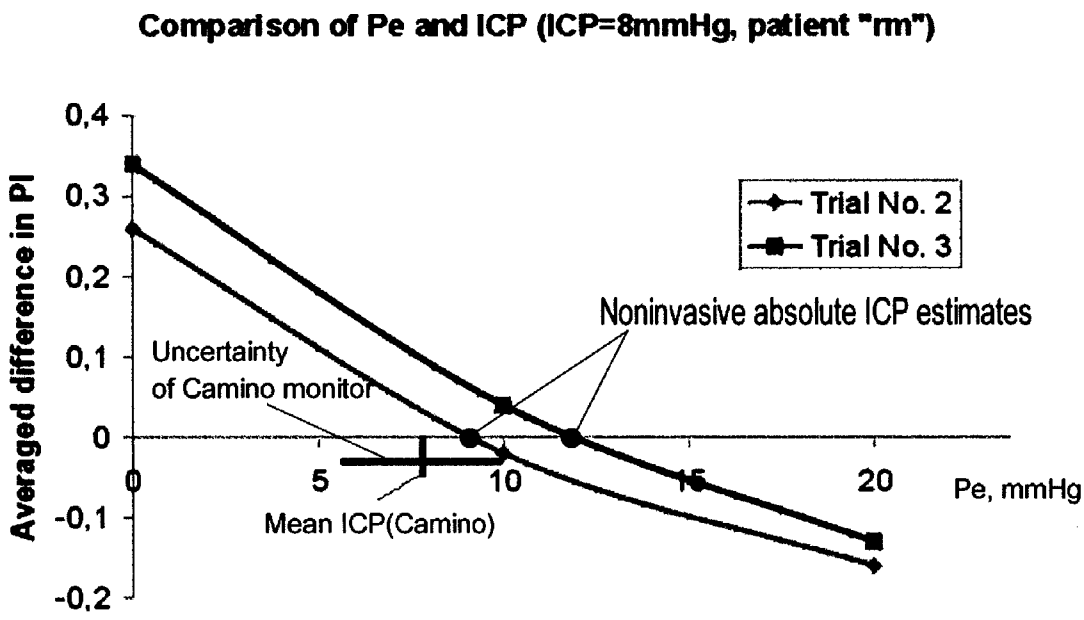


Fig. 24. The dependencies of Gosling pulsatility indexes (PI) differences (difference between intracranial PI and extracranial PI) on extracranial pressure Pe in the extracranial segment (d=40 mm) and intracranial segment (d=54 mm) of the eye artery measured in ICU applying the prototype two-depth TCD device. In the case of balance ICP = Pe, the difference of PI = 0.

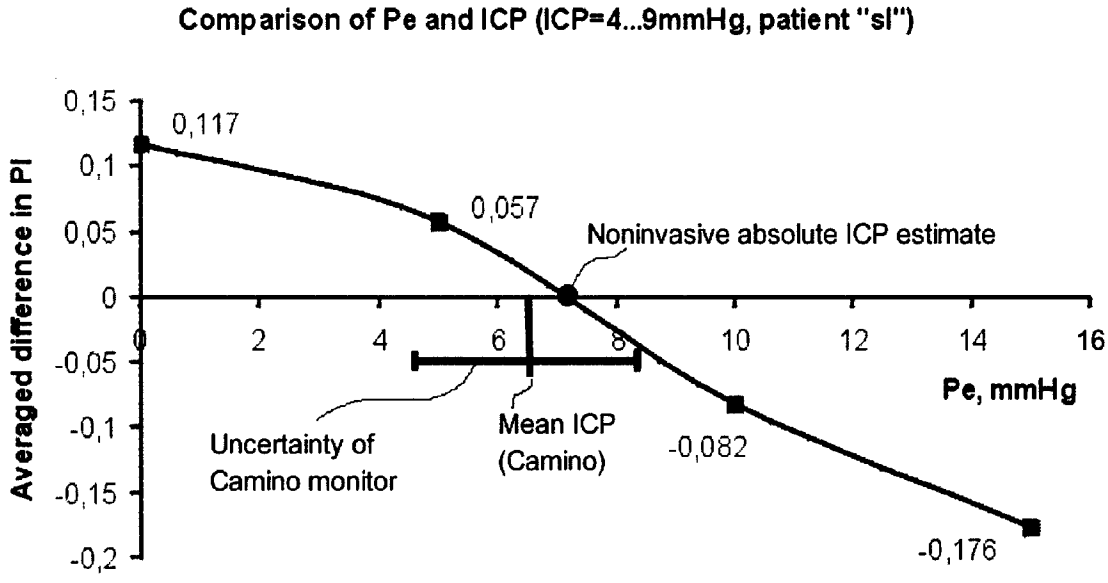


Fig. 25. The dependence of Gosling pulsatility indexes (PI) difference (difference between intracranial PI and extracranial PI) on extracranial pressure Pe in the extracranial segment (d=40 mm) and intracranial segment (d=54 mm) of the eye artery measured in ICU applying the prototype two-depth TCD device. For balance ICP = Pe, the difference of PI = 0.

The proposed and tested absolute ICP measuring technology is based on balancing of the "scales" (Fig. 21). It is not based on the measurements of the absolute values of the eye artery blood flow parameters. Because of that the non-invasive ICP measurement results do not depend on individual anatomical properties of the patient under study or an individual state of the eye artery blood flow. Balancing method (Fig. 21) does not need an individual calibration of the system "individual patient – non-invasive ICP meter". This property of proposed technology is unique.

1.6. DISCUSSION ON THE CLINICAL RESULTS OF PRELIMINARY TESTING OF THE NON-INVASIVE ABSOLUTE ICP MEASUREMENT PROTOTYPE DEVICE AND ON THE TECHNOLOGY DEVELOPMENT

The preliminary clinical results show that the prototype two-depth TCD device for absolute ICP measurement can be used in ICU environment. Two measurement methodologies could be applied in this case:
- serial measurement of blood flow parameters in the intracranial segment of the eye artery and after that in the extracranial segment of the eye artery,
- simultaneous measurement in both depths of the eye artery.

The first methodology is useful in the case of a stationary patient condition when ICP is changing because of heart pulsation and breathing. In this case it is possible to achieve the best possible signal to noise ratio in both depths and, as a result, to achieve a minimal possible random error of absolute ICP measurement.
The second methodology is the best possible when it is easy to adjust the ultrasonic transducer for simultaneous two-depth TCD measurement.
Our experience from 25 measurements of 3 ICU patients shows that both methodologies give very close values of absolute ICP measured non-invasively.
The main causes of the positive absolute systematic error of non-invasive absolute ICP measurement are the following:
- the eye artery blood pressure gradient along the optic canal. We applied mathematical modeling to predict this error. The predicted value of this systematic error is approximately 3 mmHg;
- the pressure gradient between the absolute extracranial pressure inside the flexible latex pressure chamber and the external segment of the eye artery. This gradient depends on the elastic properties (in the first place, thickness) of a latex film and depends on the stability of the fixation on the human head of the rigid part of the extracranial pressure chamber;
- the errors of two-depth TCD based comparison of similarity of the eye artery blood flow in intracranial and extracranial segments. The limitation here is the necessity for such comparison to apply blood flow parameters which do not depend on the insonation angle. Such standard parameters are pulsatility index (PI) and resistivity index (RI). Neither of these standard indexes can be obtained with necessary sensitivity and accuracy in the case of absolute non-invasive ICP measurement. We proposed and performed a computer modeling of a more sensitive index based on the insonation angle independent ratio between the mean power of upper harmonics and the mean power of the first harmonic of the pulsating blood flow.

Our limited clinical experience (25 measurements, 3 patients) of the absolute ICP measurement below the critical level of 25.0 mmHg applying PI as a balance indicator shows that the systematic error of non-invasive absolute ICP is always positive and does not exceed 20%...25% of the invasively measured mean absolute ICP value.
To decrease the errors of non-invasive absolute ICP measurement it is necessary:
- to develop an extracranial pressure chamber applying the latex film as thin as possible in order to minimize the extracranial pressure gradient;
- to develop the rigid part of the extracranial pressure chamber also in order to minimize the extracranial pressure gradient during the measurements;
- to develop a software for two-depth TCD measurement data computer analysis (PC connected with the two-depth TCD prototype device) and for the indication of intracranial and extracranial pressure balance in ICU environment;
- to develop a software for non-standard index calculation to obtain a more sensitive disbalance of blood flow in the eye artery;
- to perform absolute ICP measurements in ICU applying the indexes mentioned;
- to collect a statistically significant number of clinical simultaneous invasive and non-invasive

absolute ICP measurement data following Clinical Research Protocol No. 9912 4006, AIBS No. 990135, HSSRB Log No. A – 9676 by September 2002,
- to perform experimental evaluation of the potential accuracy of non-invasive absolute ICP meter in the situation when the TCD signal to noise ration is the best possible. In order to perform this experiment the standard echo-contrast agents (e.g., Levovist, Schering, Germany) need to be used during two-depth TCD measurements of the eye artery blood flow.

Ideally, in the final version of a non-invasive absolute ICP meter (not within the framework and budget of this project) it would be necessary to include:
- a five degree of freedom microrobotic subsystem for fast automatic spatial adjustment of the ultrasonic transducer;
- power M – mode option for spatial adjustment procedure control;
- a microprocessor for balance index calculation and indication.
Thus, a "one button" device for absolute ICP measurement could be created in the future.

2.0. NON-INVASIVE ICP / VOLUME REAL - TIME MONITORING

2.1. SLOW INTRACRANIAL PRESSURE WAVES AND CEREBROVASCULAR AUTOREGULATION MONITORING. STATE OF THE ART

Slow pressure waves in the cranial enclosure include as components both the well known intracranial pressure (ICP) waves of the cerebrospinal fluid (CSF) described in the pioneer studies of Janny [47] and Lundberg [67] and the slow blood volume (BV) waves carried by blood vessels. BV is the main cause of ICP waves. The arterial blood pressure (ABP) component is the most frequently analyzed as the cause of BV waves. It is extracted from the peripheral ABP signal (e.g. radial artery) which is accepted, under clinical conditions, to be a correlate of the intracranial ABP signal.
BV waves can be measured non-invasively applying Vittamed time-of-flight ultrasonic technology.
Pulse and respiratory waves respectively derived from cardiac and breathing activities are excluded of the slow wave definition [59].
The vascular origin of the ICP slow waves through intracranial volume variations is nowadays accepted, even if it was only demonstrated for the slowest, the A or "plateau wave" [104, 107]. The cerebral control, without precise explanation, of these periodic activities or rhythms, has been evoked at once [47, 67, 123] at least for the fastest (Lundberg B and C waves).
The inter-relationships between ICP and ABP waves, cerebral perfusion pressure (CPP), craniospinal compliance and cerebrovascular autoregulation are still controversial. From a clinical point of view, mostly the Lundberg A and B waves are used. They are also indicative of intracranial hypertension (ICH). In the management of ICH in severe head injured patients, a minimum duration of 2 minutes of ICH was proposed prior to treatment [56, 82]. More recently an ICP threshold of 20 mmHg - 25 mmHg was set [13]. However, these absolute values must be carefully interpreted as, for example, a 2-minute duration only corresponds to the longest duration B wave which may return spontaneously to a normal ICP value.
The analysis of B-waves was one of the main preoccupations of neurosurgeons and neuro-care physicians for many years. Nowadays B waves are of less importance because of the changed clinical focus on more aggressive ICP therapy; this may also be due to the current bedside environment in intensive care units not easily providing for the display and analysis of B waves. Most of the invasive ICP transducers do not distort the slow waves, but inadequate sampling and poor printer resolution can lead to wave disappearance. This technical problem may in part explain their intermittent characteristics. Historically, these slowly varying waves were defined by Janny and Lundberg from a simple visual description. Nowadays temporal and frequency domain mathematical approaches allow a more objective analysis and a semi-automatic or automatic quantification and/or detection. The frequency domain approach is more recent [38, 59, 106] and provides a concise description [62]. Mathematical tools are also used, which enhance the simple graphic analysis, for comparing slow waves between two or more signals, in particular to measure the phase lags or time-delays while attempting to quantify cerebral vasoreactivity and cerebrovascular autoregulation.

2.1.1. DEFINITION OF SLOW CEREBRAL WAVES

The slow waves are considered both permanent and intermittent, depending mainly on whether they are envisaged from a physiological or a pathological point of view, respectively. The most widely used classification for the slow ICP waves is that proposed by Lundberg and similar to Janny's . In trying to find a rationale several classifications have been proposed to clarify various types of slow waves based on the description of different morphologies or temporal patterns for B and A waves [14, 15, 59, 65, 102].

Recently a new type of classification based on a frequency approach was proposed [59]. It includes all types of pressure waves. Derived from the classical data of the ICP waves, three distinct frequency bands were created: Infra B (IB) below 8 mHz; B from 8 mHz to 50 mHz; and ultra B (UB) beyond 50 mHz up to 200 mHz. From the preliminary studies it was evident that, at least under pathological conditions, different ICP slow waves can coexist at the same time [47, 67, 109]. Sometimes they have some remarkable patterns, such as an amplitude modulation by the slowest [59] and a gradual temporal transformation from B to A waves [59, 102].

Historically, A waves were considered as intermittent pathological oscillations, also currently named "plateau wave" [47, 67] expressing an uncompensated ICH and more frequently observed with fossa posterior occupying lesions [89]. From a biomechanical point of view, today, they are linked with low compliance conditions [23]. B waves were originally considered as intermittent physiological waves of which the amplitudes increase during ICH [47] or as intermittent pathological waves linked to respiration [67]. C waves were linked to peripheral ABP waves [47, 67], stricto sensu the Mayer waves.

The pathological character of the ICP slow waves, with its therapeutic implications, is not clear. They were, and still are, considered as pathological for A waves [47, 67], for B [17] and for C waves [67, 109]. From the analysis of long-term recordings performed for active hydrocephalus, they are limited to those with definite amplitude and occurrence characteristics [11, 18, 35, 48, 55, 96, 102, 115].

For the waves most widely accepted as pathological, the plateau waves, Czosnyka et al [23] have recently shown that they are not associated with a bad prognosis in the severe injured patients. Several studies on subarachnoid haemorrhage argue that the presence of B and IB waves are evidence of vasomotor instability [40], reduced in the case of vasospasm and sedation [60] and abolished during "vasoparalysis" [40]. Venes [123] noted that in the case of ICH due to a mass effect, the presence of B waves was linked to a good outcome. From a physiological point of view, the permanence of the three types of physiological slow waves was not confirmed due to the lack of long-term recordings on healthy subjects.

Non-invasive technology for slow wave monitoring can be only used on healthy persons.

Nevertheless, the presence of B waves in healthy infants during sleep was demonstrated [125] as well as during short ICP signal recordings [59]. Indirectly they were also identified in cerebral blood flow velocity (CBFV) in healthy subjects [80]. The main hypothesis has been a permanent physiological phenomenon, amplified, hence easy to detect, during ICH and other brain-suffering conditions [26, 30, 47]. From a clinical point of view, the slow waves are mainly the evidence of the intracranial pressure dynamics, sometimes participating in the decompensation of ICH for the slowest and widest waves, like the "plateau waves". In this limited sense, they can be considered as pathological waves. In other cases, the definition of thresholds for the amplitude and for the frequency, though the latter is linked to the former [59], seems to be necessary to identify not pathological waves but pathological patterns. ABP slow waves described in peripheral arteries were well known for a long time but the terminology is still imprecise. Various authors used more or less equally such terms as Mayer, Traube-Hering, or Traube-Hering-Mayer waves. In fact, the Mayer waves or third-order waves are linked to modifications of the vascular tone, and the Traube-Hering waves or second-order waves to the respiratory movements [5, 16, 99]. The predominant frequencies of the Mayer waves can be divided into two distinct bands: the lowest from about 30 - 40 mHz to 60 - 80 mHz and the highest from about 100 mHz to 200 mHz [3, 16, 36, 46, 99, 126]. The fourth-order waves, with a frequency of 0.55 mHz were also described in pathological circumstances without ICH [16].

2.1.2. PHYSIOLOGY AND PATHOPHYSIOLOGY OF SLOW ICP / VOLUME WAVES

The analogy between the ICP and ABP slow waves is strong. Their frequency domains overlap

and according to our current knowledge their regulations are quite similar. The discrepancies could be due to the biomechanical characteristics of the vascular tree and the cranial enclosure. The ICP waves would be the result of cerebral blood volume changes of which the vascular one is predominant. The role of the systemic and intracranial vascular controls is still debated. In general, the two main influences on the appearance and occurrence of the IC slow pressure waves are the vascular bed and the compliance of the enclosure.

Time relationships between ICP and ABP slow waves are extremely important for continuous cerebrovascular autoregulation monitoring.

These time relationships are a slightly different function of the frequency bands. For the IB band, Rosner's theory [107, 108] considers that the plateau wave follows a CPP decrease induced by an ABP decrease, but the peak of ICP precedes the ABP one. The existence of a high and a low autoregulatory threshold was proposed to explain the initiation and the end of the process. At the maximum CPP drop, a Cushing phenomenon could be involved in the peripheral ABP increase.

In fact, less than one quarter of IB waves, also named vasogenic waves, have such a chronology in a non-selected large series of severe head injured patients, and in most of the cases the trough of CPP is synchronous with the ICP peak [100] . Different types of chronology between ICP, ABP, and CPP IB waves were clearly confirmed by a recent study [23], but had already been noted earlier [65, 67, 79, 109].

Rosner [108] also demonstrated that the chronology of the B waves was similar to the plateau waves. He proposed the same mechanism of regulation. Other works have noted for B and even UB waves, that the ICP can be linked to the ABP, as accepted by the Rosner theory. They can also have unorganized or synchronous relationships [85, 109], or inversion of peaks with the ABP preceding the ICP [112]. The absence of dynamic autoregulation could explain the synchronous increase of ICP and ABP during B waves [22]. In the case of intact autoregulation the ABP and ICP changes are related inversely.

Cerebrovascular autoregulation based on active variations of cerebrovascular resistance can be seen from two points of view. Schematically, the static, or classical one, corresponds to a near constant cerebral blood flow over a range of ABP or CPP values, i.e. the pressure-flow aspect, but also the capability to regulate the flow for different brain metabolism needs, i.e. the metabolic-flow aspect.

In clinical conditions only the pressure-flow aspect is assessed by ABP variations with drugs, in spite of ethical and practical bedside difficulties: hypertension with phenylephrine [58, 84, 114], or angiotensin [31]; hypotension with trimethaphan camsylate [58, 84], or labetalol [58].

Recently Dawson et al [24] proposed an alternative to drugs with mechanical manoeuvres lasting 2 min and 45 sec. The flow variations are measured directly by ^{133}Xe single–photon emission computed tomography [31, 58, 84], or indirectly by transcranial Doppler (TCD) on large vessels [24, 58, 114] assuming that their calibre is almost invariable during the procedure. This type of autoregulation is susceptible to hypercapnia, which experimentally abolishes the response leading to a passive pressure relationship [39].

The dynamic aspect of autoregulation was initially defined as rapid adaptive cerebral blood flood modifications provoked by tensional manoeuvres [1]. The comparison of spontaneous slow waves, in term of coherence and gain, was also applied in the IB domain to evaluate dynamic autoregulation [33]. These elements introduced the temporal dimension in the process of autoregulation for the pressure-flow aspect. In a broad sense, the dynamic aspect of the autoregulation can be defined as the delay between ABP or CPP variations and the adaptation of CV or CBF [20, 33, 34].

The CO2 level influences the dynamic autoregulation, the amplitude is lower and the delay is longer during hypercapnia and inversely during hypocapnia [2]. Several techniques have been proposed to quantify this dynamic process. They fall into three types.

The first uses artificial manoeuvres, i.e. carotid compression [20, 34], release of a tight cuff [1,

87], slow breathing [25], Valsalva manoeuvre [120] and orthostatic hypotension [90].
The second type analyses intermittently the inter-relationship between B waves of a couple of signals (i.e. ICP, ABP, SJO2, CBFV) by calculation of a cross-correlation coefficient [112], a regression line [94] and a phase shift angle [10].
The third type analyses continuously the inter-relationship of B waves between CPP and CBFV [21] and between ABP and ICP [22, 63].
The links between dynamic autoregulation and the slow pressure waves are revealed by several convincing data which support the principle that the time delay measured between ICP and ABP slow waves could be due to and/or modulated by the autoregulation. The chronology and the duration of the time delays between slow waves on ICP and related signals are of the order of those of the dynamic autoregulation [1, 2, 10, 25, 29, 53, 63, 109, 112]. Czosnika et al [23] have shown that IB waves are associated with dynamic autoregulation. There are links between the evaluations of dynamic autoregulation through artificial manoeuvres and spontaneous oscillations [95] and between dynamic and static autoregulation [119]. Static autoregulation can be present during plateau waves [79, 107] and IB waves may occur regardless of static autoregulation [79].
Vittamed non-invasive slow wave monitoring technology can replace invasive ICP slow wave monitoring. The autoregulation state can be continuously and non-invasively identified as a cross-correlation between non-invasively measured cerebral blood volume slow waves (Vittamed time-of-flight technology) and ABP slow waves.

2.1.3. SLOW INTRACRANIAL PRESSURE WAVES

For B and C waves because of their durations (from five seconds to two minutes) only the vascular bed seems to explain these biological events. Pioneer works have proposed the vascular origin of these waves [47, 67, 7]. Recent B wave data obtained from laser Doppler microcirculation flowmetry under pathophysiological conditions [91] and in CBFV in healthy people [80] indicate the same. The vascular origin of A waves was demonstrated [79, 104] even if the implication of concomitant CSF flow modifications is unclear [41-43, 104]. Only for IB and B waves, two apparently different theories are evoked for the control of these vascular volume oscillations, i.e. the ABP-based and the neuropacemaker-based. The former is the Rosner theory [108]: the waves are provoked by ABP variations dependent on the level of cathecholamine; temporal evolution is regulated by autoregulation thresholds and the Cushing phenomenon induced by upper brainstem ischemia. During ICH it was demonstrated that there is an increase of sympathetic activity, worsened by ABP hypotension [51]. The Cushing response is an unspecific reaction of the brainstem which is triggered by factors other than ICH: ischemia, hypoxia, hypercarbia [68]. The sympathetic cardiovascular tone is also controlled in the right insular lobe [92]. This could explain the fluctuations in ABP, and potentially of slow waves, in spite of dysfunction of the brain stem and/or ICH. The neuropacemaker-based theory is based on the central origin and control of these oscillations. It involves the cholinergic basal forebrain, the brain stem, the cingular cortex and the reticular formation of the medulla [44, 70-75, 121]. They could correspond to the vasomotor neurovegetative central centres, possibly different for each frequency band [70, 71], and the specific brain pathways of the cerebral vessels. The ABP-based and the neuropacemaker-based theories could correspond respectively to the pathophysiological side and to the physiological side of the same phenomena, the ABP wave. The waves could be modified by the mechanical status of the craniospinal enclosure and by the vasoreactivity, in particular the autoregulation, and by the reaction to distortion or to ischemia of the nervous centres. The control centres and pathways could be the same for both theories.

2.1.4. SLOW ARTERIAL BLOOD PRESSURE WAVES

Little data is available on slow intracranial blood pressure waves. There are B waves in cerebral blood flow of patients and healthy subjects [28, 66, 80, 86] and under experimental conditions on microcirculation [7]. Experimentally there are also UB waves in micro circulation [27, 49, 81, 93]. The sympathetic cervical system and the level of ABP influence the occurrence of UB waves [49, 93]. It is interesting to note that the neurovegetative system is also involved in the extension of the low and high limits of cerebral autoregulation [69]. An intrinsic muscular parietal activity of cerebral vessels was also described in the B band [6]. On the other hand many studies in the cardiovascular domain have documented the presence, origin, and regulation of slow extra-cranial ABP waves. Beyond the definitions of the frequency bands the slow blood pressure waves are ubiquitous, directly visible in the systemic circulation and also in the eye enclosure [118]. As for the slow ICP waves they are considered to be both a physiological and a pathophysiological permanent phenomenon attributed to vaso- and chemocentral feed-back controls, central spinal oscillators and ischemic central oscillations [3, 36, 99]. The permanency, or at least sustained episodes, of the Mayer waves during pathological and almost physiological circumstances of ABP fluctuations [78, 99], suggests a physiological origin, modulated and/or triggered by pathological or physiological conditions of the vasomotor sector. ABP slow waves are linked to heart beat fluctuations [3]. A non-linear control related to respiratory variations was proposed [46].

2.1.5. SLOW CEREBRAL WAVES AND OTHER BIOLOGICAL PARAMETERS

Several other biological signals are linked through their frequency bands to the slow intracranial pressure waves. The ICP slow waves are linked to neuronal activities in the spinal cord [74], the brain stem [44, 52, 70-72, 121], the hypothalamic nuclei [70, 71, 110] and in the cingular cortex [70]. Studies have also shown oscillations of brain metabolism in B and UB bands [27, 81, 124]. Peripheral blood gas concentrations of CO2 and O2 have oscillations in the B band inconsistently linked with ICP B waves [30, 50, 67]. The relationship of the ICP B waves with the Cheyne-Stokes respiration has been well documented for a long time [30, 47, 67]. In most of the cases the ICP peak coincides with the widest breathing movement [30]. It is interesting to note that different rhythms of this respiration [57] are included in the B frequency band. Other respiratory patterns in the B band are also linked with ICP B waves [32]. Janny [47] described the links between ICP UB waves and respiration. It was also known [67] that artificial ventilation can either provoke the disappearance of high amplitude B waves or modify the pattern. During both pathological and physiological circumstances, ICP and ABP waves in IB and B bands have shown an increase in activity during REM sleep [8, 19, 37, 52, 55, 77, 83, 97, 110, 115, 127]. The vascular control by a sympathetic activity could be the link between waves and sleep [8, 19, 64, 67]. Loss of consciousness during coma and sedation seems to reduce the amplitude of B and IB waves [60]. There are also links between SJO2 and ICP slow waves, dramatic changes in SjO2 during ICP B waves [101] and inconsistent fluctuations of SjO2 [50, 101, 105] during IB waves. Studies have shown that a decrease in craniospinal compliance modifies the amplitude and frequency of the slow ICP waves, in particular increasing B wave amplitude [26, 61, 122]. Indirectly Allen and Bunt [4] have found slow oscillations of compliance in IB and B bands, and if we consider that they are spontaneous, shown the complex reciprocal influence of waves and compliance. Several other triggering factors have been identified for B and IB waves: experimental ABP hypotension [53], a decrease in CPP regardless of the cause [107], and an increase in CSF outflow resistance [41-43, 122] which set off a response as excepted from the Rosner theory. Clinically decreasing ABP and CPP [108] have similar effects. Experimentally, the influence of anaesthetics and ABP on the frequency

and amplitude of B waves is debated [45, 49].

2.1.6. CLINICAL IMPLICATIONS

Two main application domains emerge from the data carried by the slow cerebral pressure/volume waves, i.e. the assessment of intracranial volume-pressure relationships which has been proposed since 1989 [106] and the quantification of vasoreactivity, in particular, the cerebral autoregulation. The knowledge of vaso (auto) regulation status could be of interest mainly in the management of ICH, whatever the cause, and after traumatic head injury. For the latter, ICH and impairment of cerebrovascular reactivity are well known causes of cerebral ischemia [117]. But the prognostic value of the loss of static autoregulation [12, 31, 114] or dynamic autoregulation [88, 111, 113] during a severe or mild head injury is not clear. In the clinical environment the interpretation of biological parameters is rarely univocal, in particular, the vascular ones which are dependent, among others, on dynamic and static CBF autoregulation, active and passive arteriolar vasodilatation [98], false static [103], and pressure-based and metabolic-based autoregulation. This could explain the discrepancy in prognosis. The temporal analysis of the relationship between ICP and ABP B waves, as a marker of impaired dynamic autoregulation, seems to be very promising [21, 22].
The second clinical domain of application is ICH, but the pathological role of slow ICP waves is not clearly identified. One exception is the high amplitude and/or long duration waves which can decrease the CBF either locally or in the entire brain by reducing the CPP and/or reducing microcirculation due to a high intraparenchymal pressure. Monitoring the waves to detect and to treat these phenomena appears to be indicated, but the threshold, duration or range prior to treatment remain to be identified even if durations of 5 min [82] or 15 min [23] have been proposed.
Nowadays both invasive ICP and ABP monitoring are often used to determine the CPP bringing us back to the complexity of their relationships in wave terms. Close to CBF, CPP slow waves monitoring could be of interest. As shown in the important literature published earlier, the quantification of the slow pressure waves also seems to be useful in the treatment of hydrocephalus to determine good patient outcome for shunting with the rationale that the ICP slow wave activity is linked to the craniospinal compliance. Recent works [9, 29, 54] continue to study this approach, as an alternative to the CSF dynamic explorations calculating the CSF outflow resistance and the craniospinal compliance. Even so, the definition of amplitude and frequency thresholds and the integration of the related physiological controls seem to be a necessary condition. A decrease in B waves was proposed as a goal in the treatment of hydrocephalus [116], however, the pathological character of the waves is yet to be demonstrated.

2.1.7. NECESSITY OF CONTINUOUS NON-INVASIVE CEREBROVASCULAR AUTOREGULATION STATE MONITORING AFTER TRAUMATIC BRAIN INJURY (TBI)

The elastic properties of intracraniospinal components constitute a very important variable involved in the regulation of cerebral blood flow (CBF). In TBI cases in up to 29.5 % of patients a constant or even reduced CBF was detected simultaneously with median increase in ICP and synchronous median increase in ABP. This phenomenon has been called false autoregulation or pseudoautoregulation [128].
From the point of view of control systems theory the cerebral autoregulation which is based on the control of the caliber of arterioles by CPP changes is an autoregulation system with a negative feedback. The pseudoautoregulation is the result of passive caliber decrement of venules and venous vessels as a reaction to cerebral arterial blood volume increment or

interstitial fluid volume increment in the case when the arterioles are absolutely dilated. This kind of cerebral blood flow regulation is the regulation with feedforward.
When the autoregulation feedback is impaired the protective vasoconstriction of arterioles is partially or completely lost and, therefore, increases in ABP are freely transmitted to the capillary bed. If autoregulation is intact, either no changes in estimated CBF or only very small ones are expected when increasing ABP within the limits of autoregulatory curve.
A wide variation in autoregulatory status in patients with severe head injury makes the treatment based on targeting CPP far from optimal. According to this reasoning, when patients have a predominantly diffuse brain injury and exhibit the phenomenon of false autoregulation the Lund approach may be an option of patient treatment. The Lund approach is totally opposite to the targeting CPP approach. The Lund approach is based on the use of permissive low CPP if brain oxygen supply is sufficient. The application of different treatment strategies and fine - tuning the management of increased ICP can only be rationally applied if therapeutic decisions are based on the accurate knowledge of the autoregulatory status of the patient. In order to decide which approach of TBI treatment for one or other autoregulatory state of one or another patient is suitable, it is necessary to use *continuous cerebrovascular autoregulation state monitoring* [20-22, 59-63, 122, 128].
The non-invasive technology for continuous non-invasive cerebrovascular autoregulation state monitoring is mostly beneficial in this case.

2.2. VITTAMED TIME-OF-FLIGHT PROTOTYPE DEVICE FOR NON-INVASIVE ICP / VOLUME SLOW WAVE REAL-TIME MONITORING

A technology for real–time elimination of ultrasonic signals delay in extracranial tissues and skull inside the acoustic path as well as the compensation of possible Doppler shift of ultrasonic signals propagating through the parenchymal acoustic path has been developed. The Vittamed time-of-flight prototype device with automatic real - time and *in situ* elimination of ultrasonic signal delays in the extracranial tissues and skull was designed and manufactured. The software procedures for automatic Doppler shift elimination are also included. This is the device which directly measures the time-of-flight of super short ultrasonic signal which propagates along the transintracranial acoustic path from one internal surface of the skull to the other internal surface of the skull. Also, the new 1.5 MHz ultrasonic transducers for such option have been designed and manufactured. The new transducers include the PVDF film layers which are used to receive echo signals from internal surfaces of dura mater or skull. The transducers are not spatially focused and because of that do not create the areas inside the brain with concentrated heating of intracranial components by acoustic energy.
The virtual panels of the non-invasive Vittamed time-of-flight prototype device are shown in Fig. 26, 27.
The main output parameters of a non-invasive Vittamed time-of-flight device which limit the duration of continuous non-invasive monitoring are the following:
- acoustic output power;
- duration of output acoustic pulses;
- repetition period of output acoustic pulses.

Fig. 28 a) and b) illustrate the output acoustic signal of the Vittamed device (Fig. 28 a)) with acoustic power P_{out} = 22.5 mW compared with the output acoustic signal of standard TCD device Multi-Dop X4 (DWL, Germany), which is approved by FDA as safe for the patients. The output power of TCD device Multi-Dop X4 is 90 mW (burst 3 mm).

Fig. 26. The virtual panel of the non-invasive Vittamed time-of-flight prototype device. Signals s2(t) and s4(t) are ultrasonic echo signals from the internal surfaces of the skull bone. Signals s3(t) and s6(t) are ultrasonic signals propagated from one side of the human head to the other side. Signals s2(t) and s3(t) are obtained when transmitting ultrasound from the left to the right side and signals s4(t) and s6(t) - when transmitting in the opposite direction. Vertical yellow windows are used for the selection of zero crossing points of the signal functions

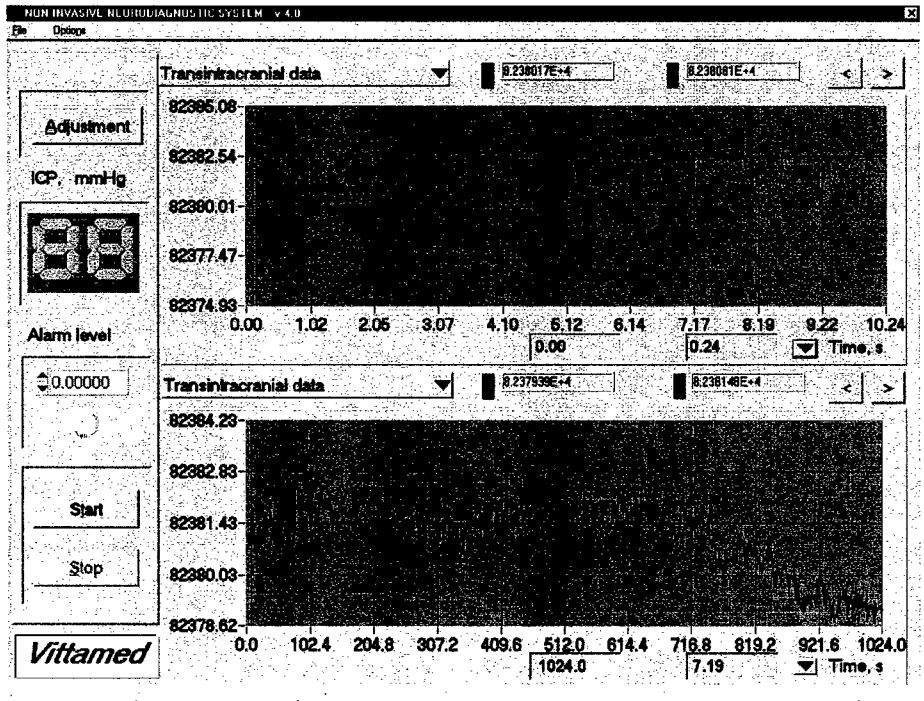
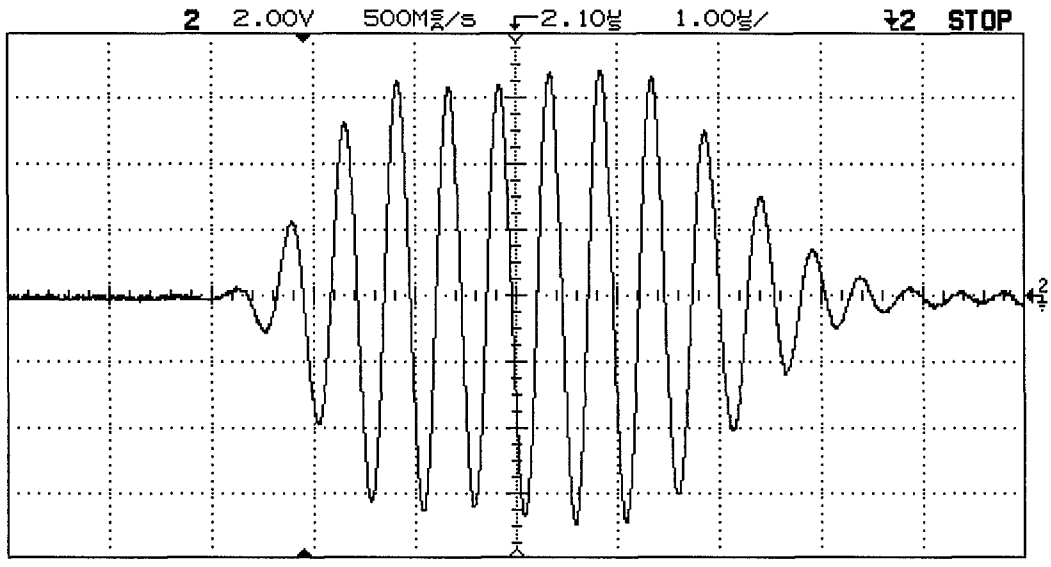
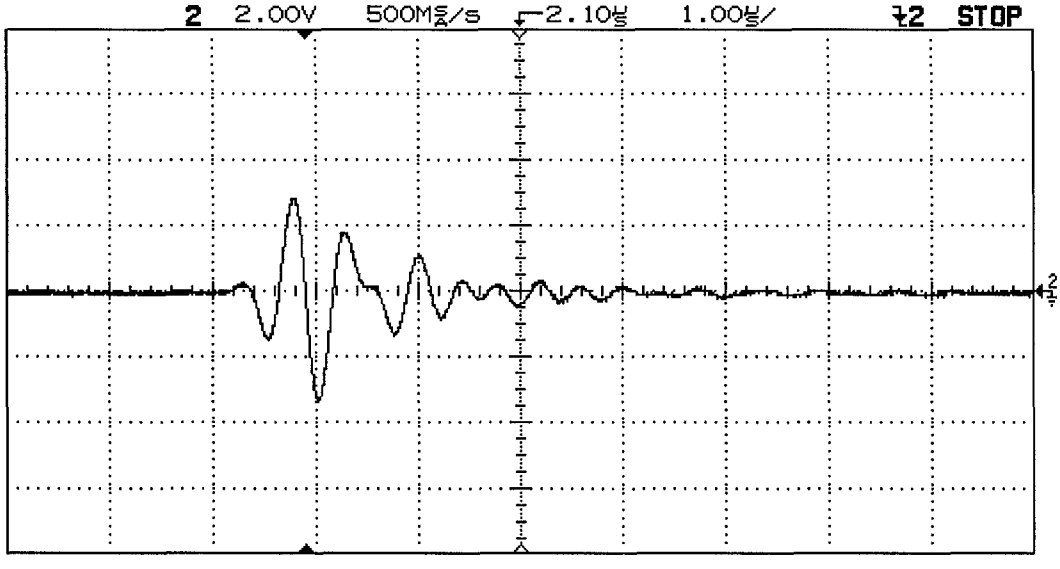


Fig. 27. The virtual panel of the non-invasive Vittamed time-of-flight prototype device: the upper window is for the display of intraparenchymal blood volume pulse waves inside the transintracranial acoustic path (all dynamic phenomena in external tissues are compensated automatically in real-time and *in situ*), the lower window is for the monitoring of slow waves and slow changes monitoring (also all extracranial phenomena, too, are compensated)



a)



b)

Fig. 28. Illustration of the output acoustic signal of Vittamed device (b) in comparison with output signal of standard TCD device Multi-Dop X4 (DWL, Germany) (a). The output power of TCD device Multi-Dop X4 is 90 mW (burst length 3 mm) (a). The output power of the Vittamed device is 22.5 mW (b)

The repetition period of Vittamed device output pulses is 1 kHz. The repetition period of TCD device is 12 kHz. Because of a much shorter duration of output pulse of the Vittamed device as compared with TCD device Multi-Dop X4 and because of 12 times lower repetition period of output pulses and also because of 4 times lower acoustic output power of the Vittamed device, the output energy of the Vittamed device is approximately 180 times less than the same parameter of Multi-Dop X4. Because of that the Vittamed device can monitor continuously and safely for a patient during 120 hours without interruption. The duration of monitoring by applying TCD devices is limited by approximately 40 minutes because of heating of intracranial tissues by spatially focused insonation.

2.3. CLINICAL TESTING OF REAL – TIME AND *IN SITU* COMPENSATION OF EXTERNAL TISSUE HEMODYNAMICS IN THE VITTAMED TIME-OF-FLIGHT PROTOTYPE DEVICE

Clinical testing of real–time and *in situ* compensation of external tissue hemodynamics in the Vittamed time-of-flight device was performed in ICU on TBI patients during simultaneous invasive and non-invasive ICP monitoring and also during continuous non-invasive autoregulation monitoring following the requirements of Clinical Research Protocol No 9912 4006, AIBS No 990135, HSSRB Log No A-9676.

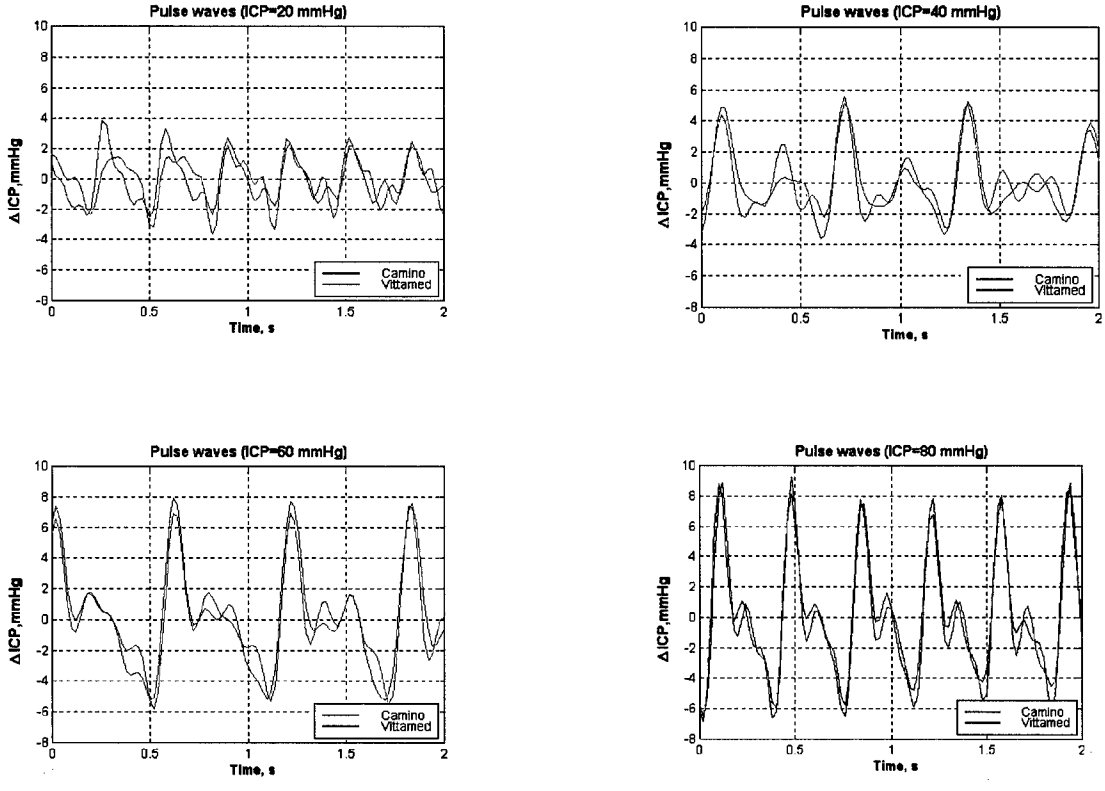


Fig. 29. Simultaneous invasive (Camino) and non-invasive (Vittamed with external tissue hemodynamics compensation) records of ICP pulse waves when mean ICP = 80; 60; 40; 20 mmHg.

The results of external tissue hemodynamic compensation on non-invasively recorded pulse wave shapes are shown in Fig. 29. The achieved is quite a good similarity between the shapes of invasively and non-invasively recorded pulse waves in different pathophysiological conditions of TBI patient (mean ICP from 20 mmHg until 80 mmHg).

The slight differences in shapes could be explained by different nature of local and focal invasive parenchymal ICP measurement and much more global and not focal non-invasive measurement.

The positive effect of extracranial tissue blood volume dynamics and possible Doppler shift compensation on absolute invasive and non-invasive ICP data similarities is shown in Fig. 30 - Fig. 32. The achieved difference between absolute invasive and non-invasive ICP data in the presented cases was within the error corridor +/-2.0 mmHg. It is necessary to mention that the errors of both devices (Camino and Vittamed) are within this error corridor because the uncertainty of Camino data is also +/-2.0 mmHg. Also it is necessary to mention that calibration of Vittamed monitor was performed using Camino monitor and linear conversion of non-invasively measured ultrasound speed data into absolute ICP values.

Simultaneous invasive and non-invasive recording of slow ICP / volume waves is illustrated in Fig. 33. The moving cross - correlation factor of slow waves (presented in Fig. 33) is shown in Fig. 34. The achieved cross – correlation $R_{C/V} = 0.92 \ldots 0.94$ (Fig. 34) is very high. This result is a clinical evidence that invasive slow wave monitoring can be replaced by non-invasive slow wave monitoring for estimation of cerebrovascular autoregulation state. To evaluate the similarity of invasive and non-invasive continuous autoregulation monitoring data we used slow wave methodology and the technique illustrated in Fig. 35.

The selection of slow B waves from raw data of invasive and non-invasive monitors was performed applying digital band pass filtering and specially designed software. This software also performed the continuous moving calculation of cross – correlation factors between invasively recorded ICP and ABP slow waves (R_I) and also between non-invasively recorded intraparenchymal blood volume slow waves and ABP slow waves (R_N).

We have recorded until now 22 sessions of cerebrovascular autoregulation continuous invasive and non-invasive monitoring in ICU on TBI patients. 12 sessions were shorter than one hour because of monitoring interruptions by patient treatment procedures.

The achieved similarity acceptable for clinical practice of invasive and non-invasive autoregulation monitoring data is illustrated in Fig. 36 – Fig. 39. It is important to mention that cross-correlation of non-invasively recorded intraparenchymal slow B waves and ABP slow waves is reflecting pathophysiological dynamic of cerebrovascular autoregulation in the same way as invasive slow wave monitoring (Fig. 36 – Fig. 39). The non-significant for diagnosing of autoregulation quantitative difference of invasive and non-invasive cross-correlation monitoring data (Fig. 36 – Fig. 39) can be explained by too local and focal nature of invasively recorded slow ICP waves. Non-invasively recorded slow B waves reflect the blood volume dynamic along the intraparenchymal acoustic path which is crossing the brain, i.e. non-invasively recorded data are much more global.

Very important clinical result is shown on Fig. 37. Optimal adjustment of SaO2 and ETCO2 in this case "switched on" the intact cerebrovascular autoregulation. Both invasive and non-invasive autoregulation monitoring techniques clearly show (Fig. 37) the same dynamic of transient process of intact autoregulation restoration.

The clinical study is continuing and will be completed during the next year when 52 or more invasive and non-invasive autoregulation monitoring one hour periods will be recorded and statistical significance of the similarity between invasive and non-invasive monitoring will be achieved.

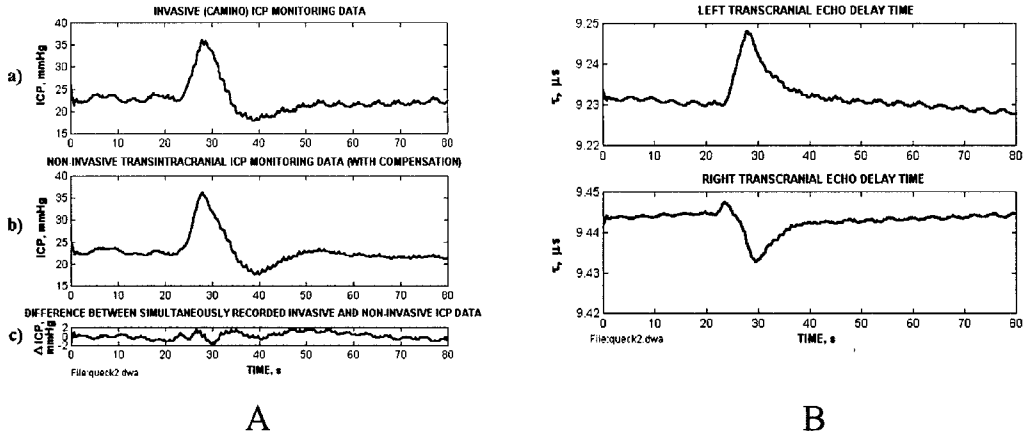


Fig. 30. Simultaneously recorded invasive and non-invasive ICP data in ICUwith real- time compensation of external tissues and skull acoustic properties: reactions to Queckenstedt test (A, B). Invasive ICP monitor (Camino) was used for linear calibration of non-invasive ICP monitor

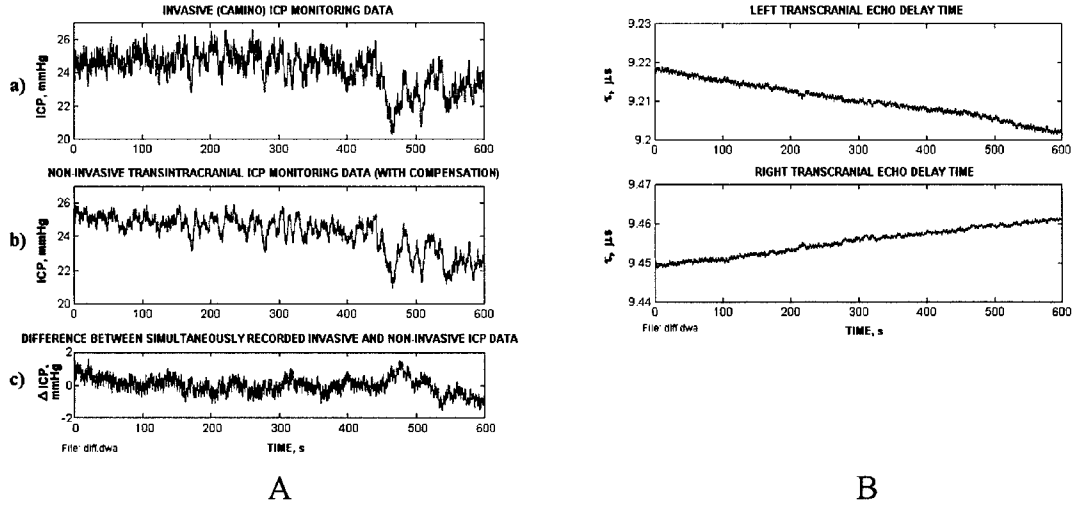


Fig. 31. Simultaneously recorded invasive and non-invasive ICP data in ICU with real time compensation of external tissue and skull acoustic properties (A, B): ICP values are close to the critical ICP level 25.0 mmHg. Invasive ICP monitor (Camino) was used for linear calibration of non-invasive ICP monitor

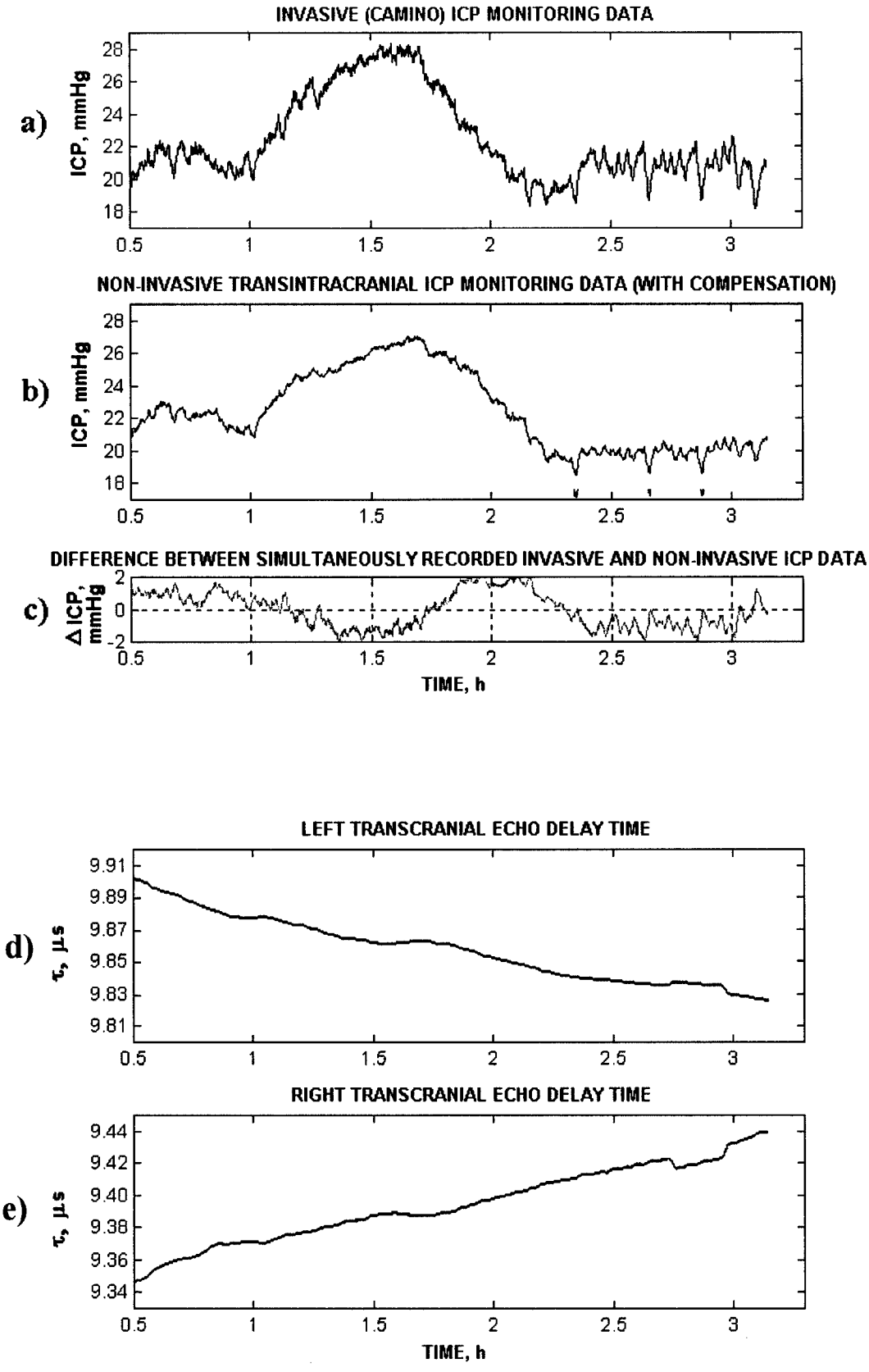
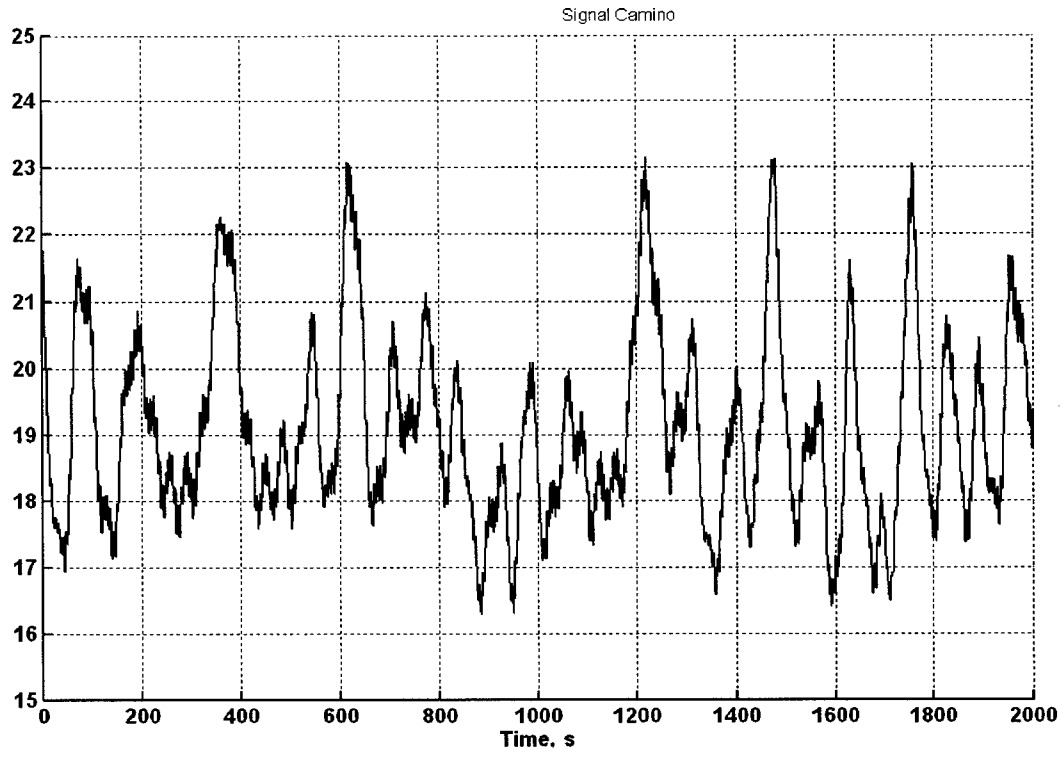
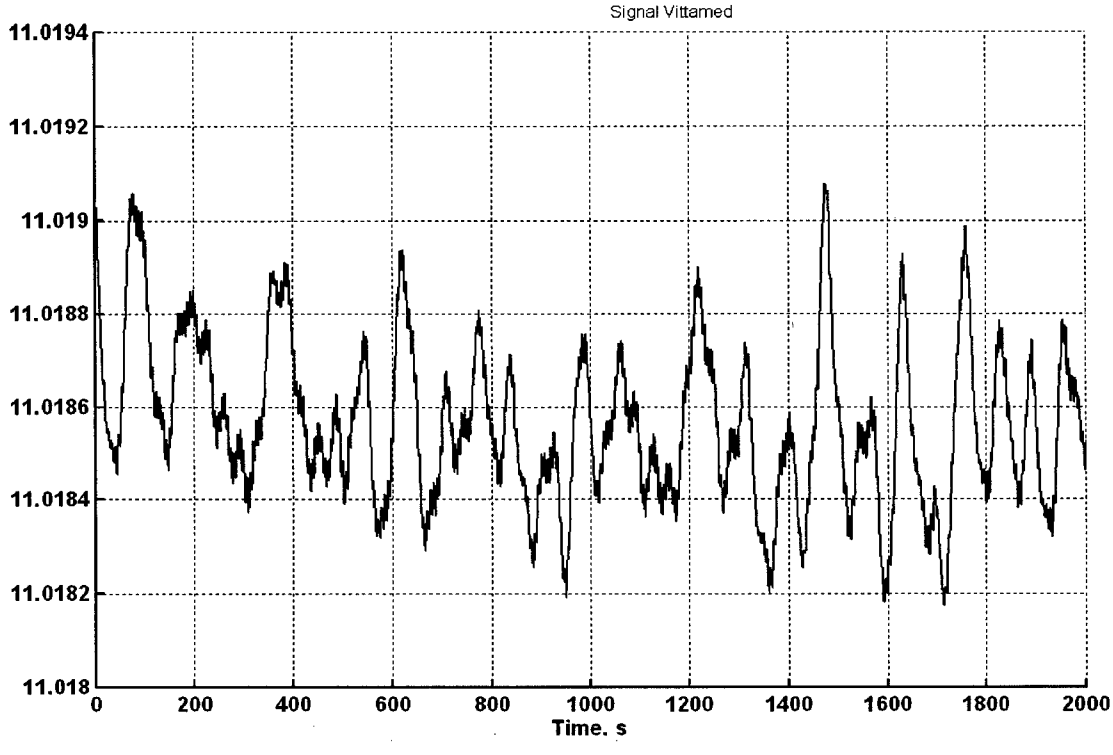


Fig. 32. Simultaneously recorded invasive (Camino) and non-invasive (Vittamed) ICP data in ICU with real time compensation of external tissue and skull acoustic properties (patient with TBI). Invasive ICP monitor (Camino) was used for linear calibration of non-invasive ICP monitor



a)



b)

Fig. 33. Continuously invasively (a) and non-invasively (b) recorded slow ICP and intraparenchymal blood volume slow waves

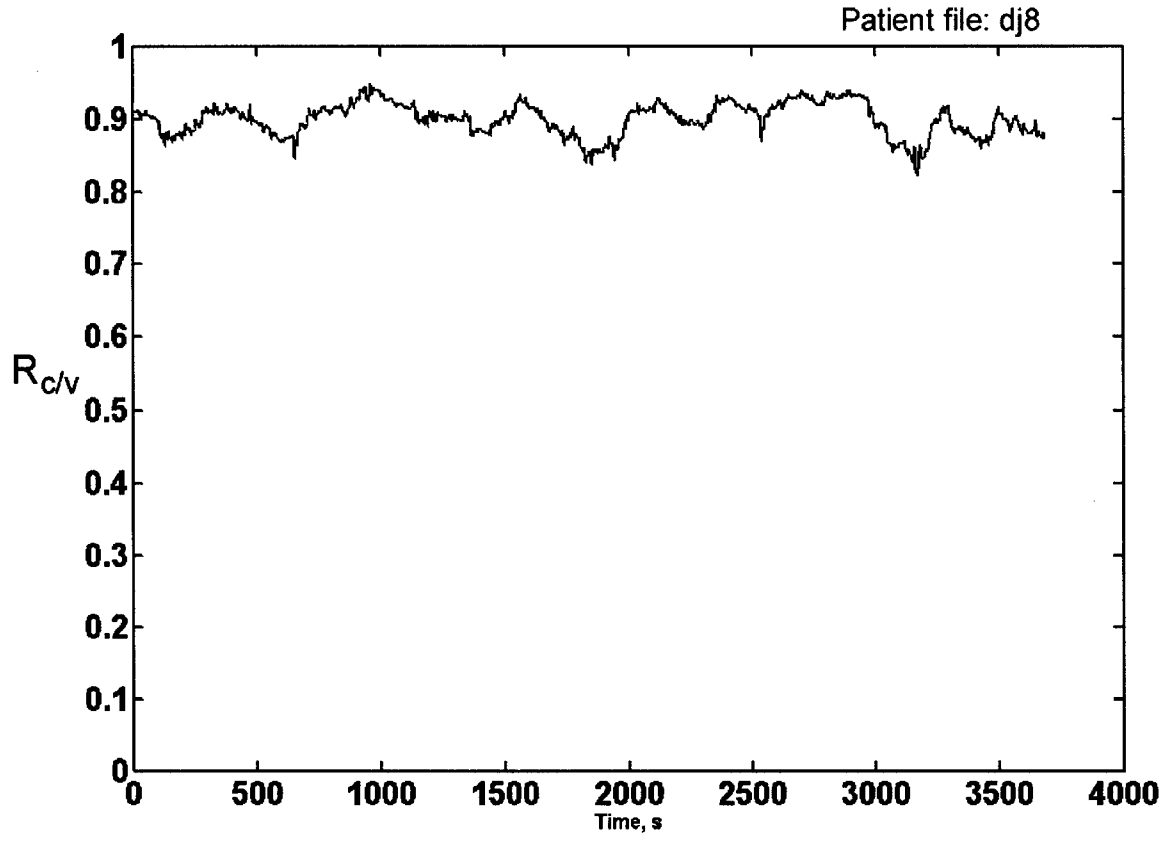
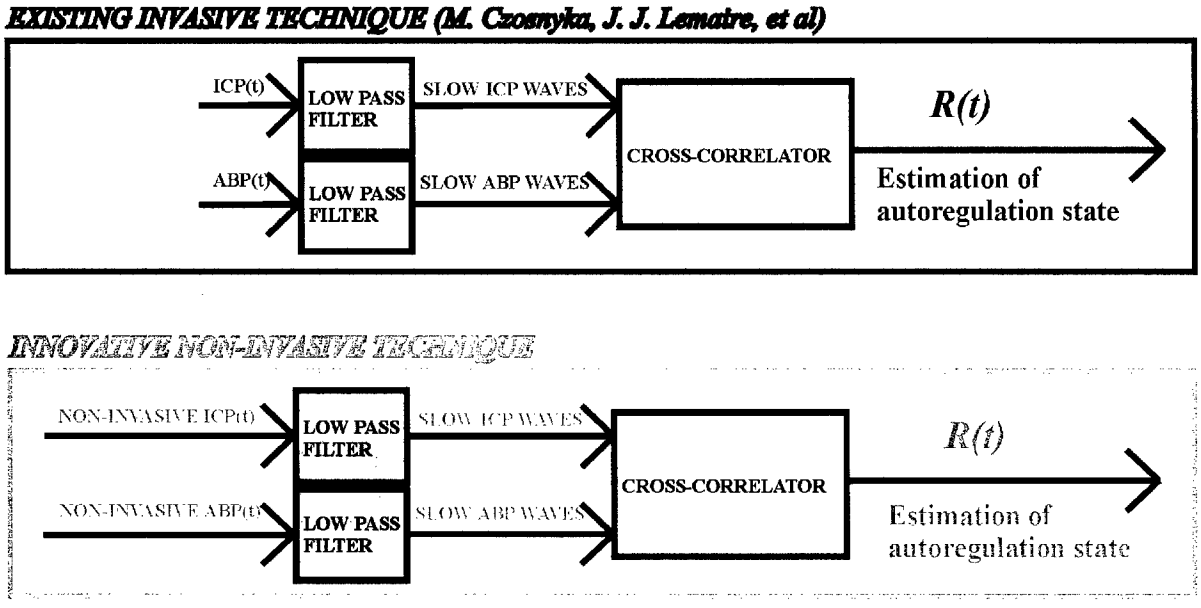
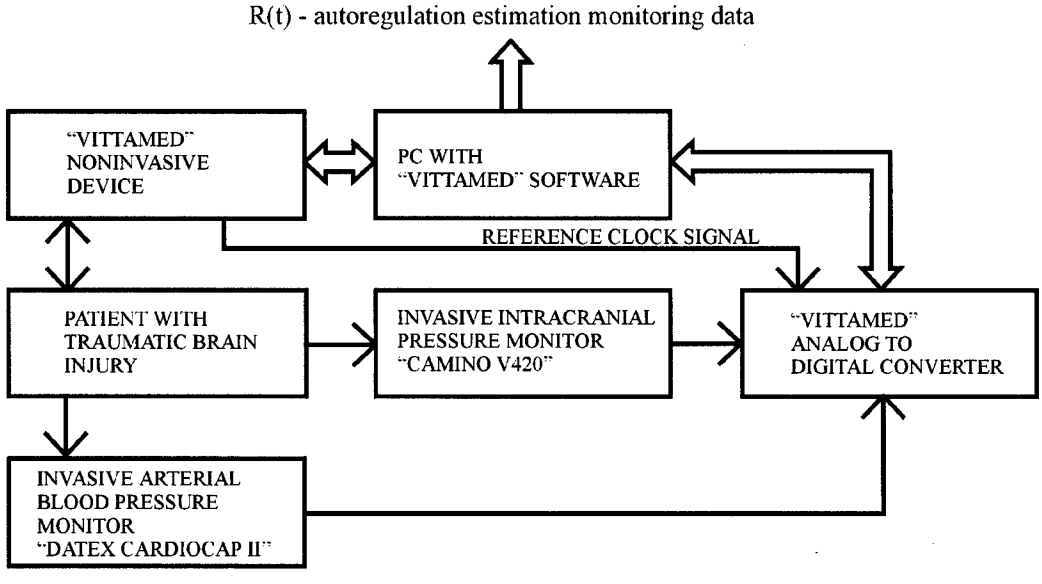


Fig. 34. Correlation factor between invasively (Camino) and non-invasively (Vittamed) measured slow ICP / volume waves (continuous 1-hour monitoring)



Impaired autoregulation: R(t) positive until +1.0.
Intack autoregulation: R(t) negative until -1.0.

a)



b)

Fig. 34. Structure of estimation technique of cerebrovascular autoregulation state (a). Structure (b) for simultaneous monitoring of autoregulation state applying existing invasive technique (Camino and Datex monitors) together with innovative non-invasive technique (Vittamed)

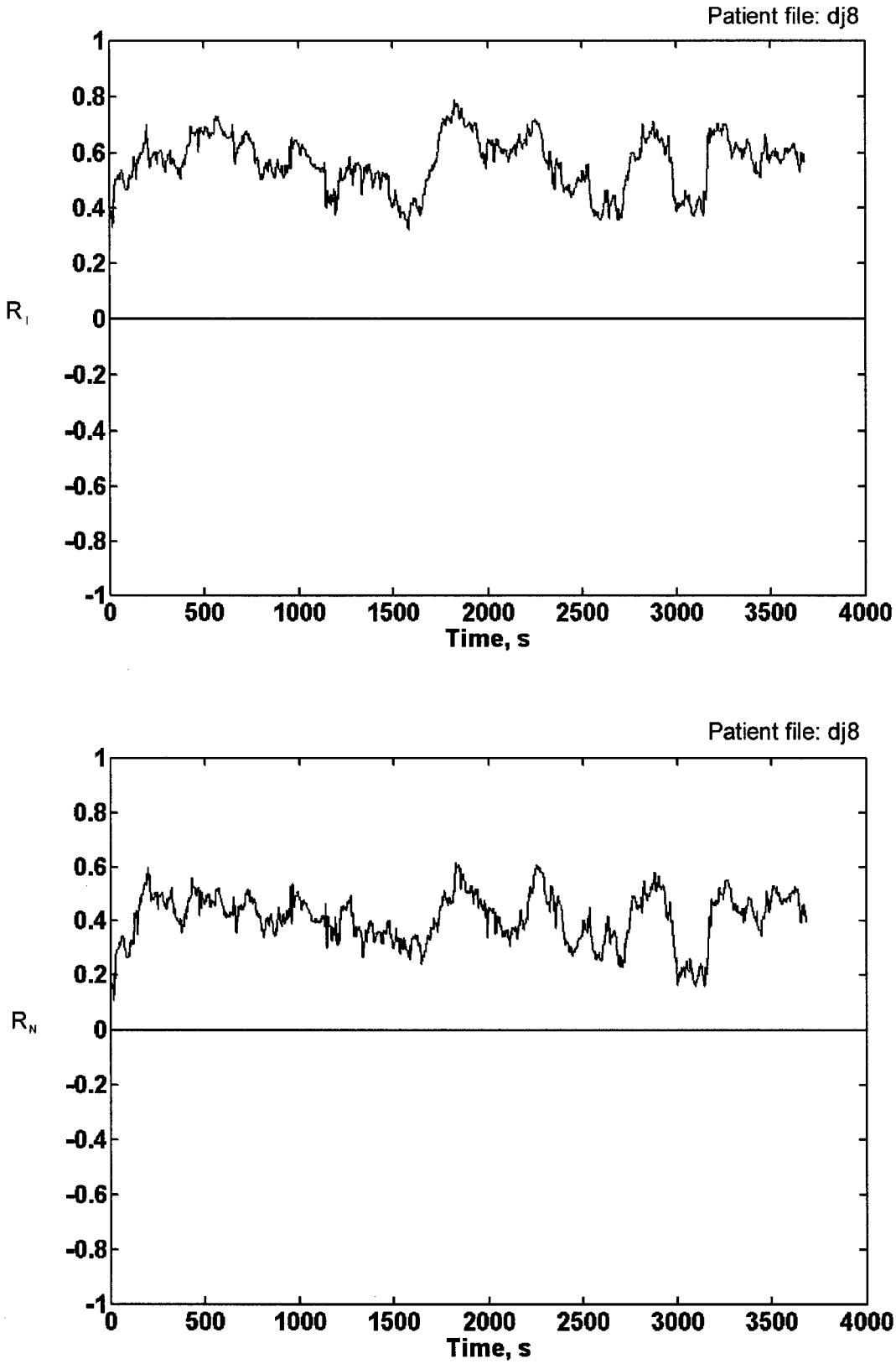


Fig. 36. Cross - correlation factor R_I between invasively recorded ICP and ABP slow waves and cross - correlation factor R_N between the same non-invasively recorded waves (ICU patient with impaired cerebrovascular autoregulation, 1-hour continuous monitoring)

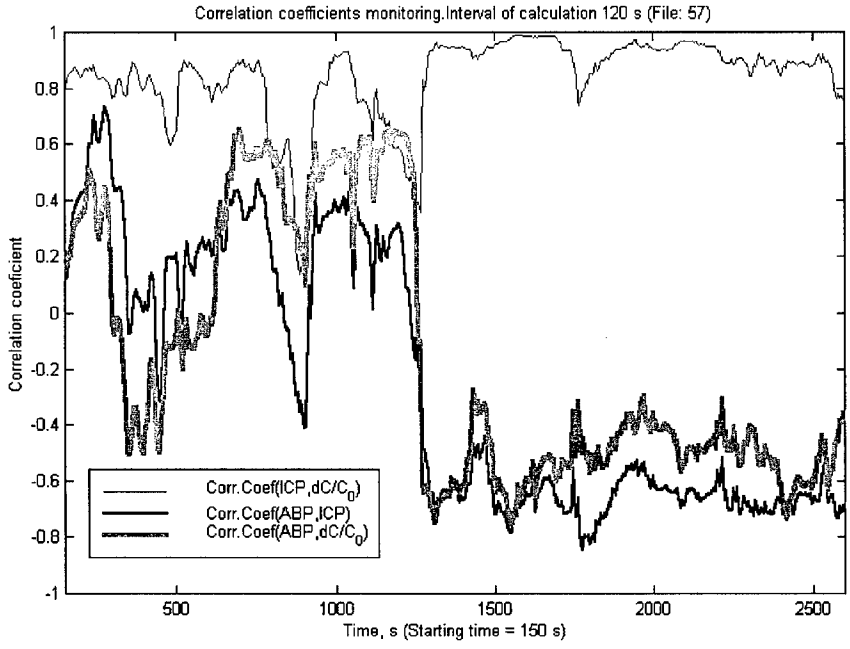


Fig. 37. Cross - correlation factors between invasively recorded ICP and ABP slow waves (blue line), between the same non-invasively recorded waves (green line) and between the same ICP and non-invasively recorded waves (red line). ICU patient with intact autoregulation after optimizing of ventilation, continuous monitoring, SaO_2 was changed from 97% to 99% and $ETCO_2$ was changed from 31mmHg to 28 mmHg at time moment t = 1000 s

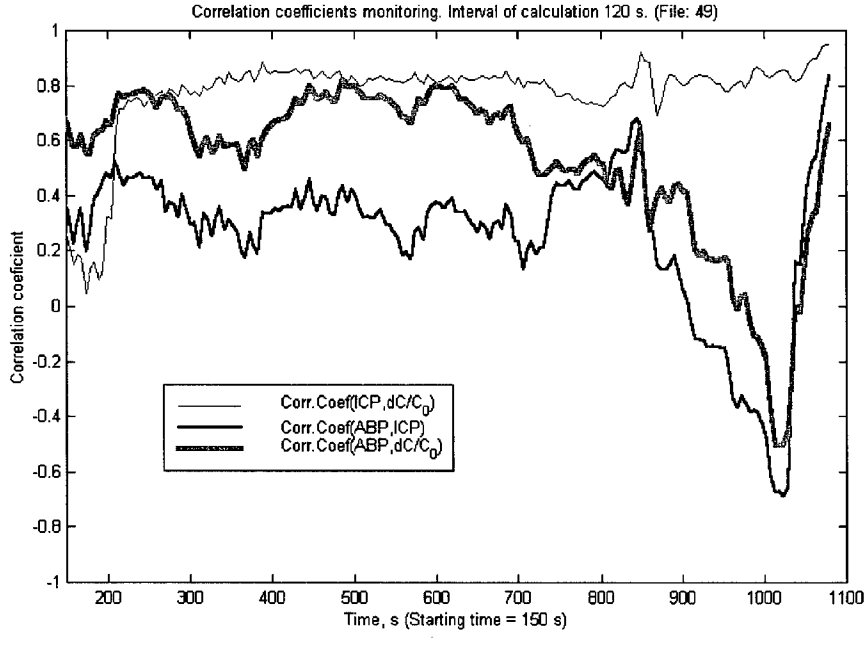


Fig. 38. Cross - correlation factors between invasively recorded ICP and ABP slow waves (blue line), between the same non-invasively recorded waves (green line) and between the same ICP and non-invasively recorded waves (red line). ICU patient with impaired autoregulation, continuous monitoring, spontaneous variation of cross-correlation factors within time interval 850 s until 1100 s

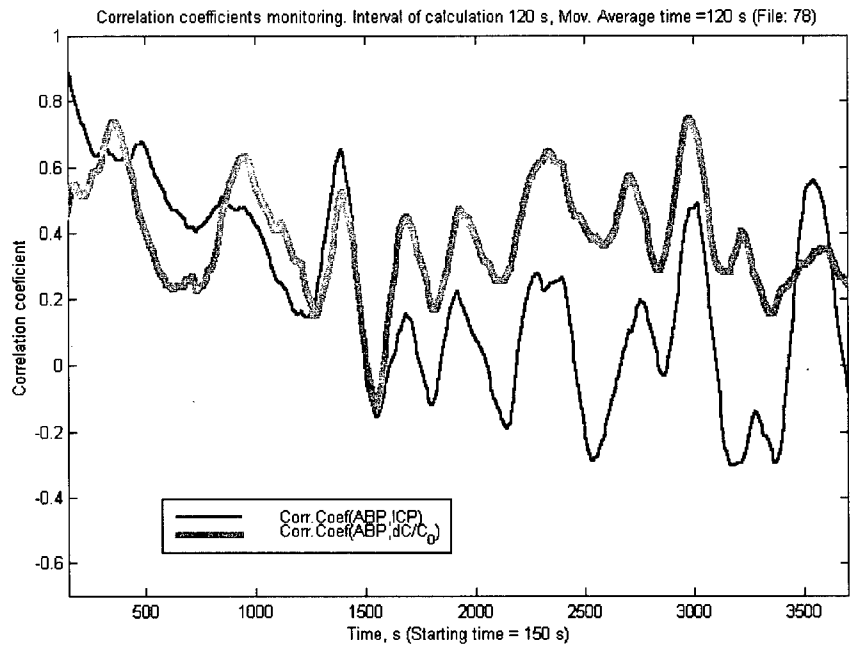


Fig. 39. Cross - correlation factors between invasively recorded ICP and ABP slow waves (blue line) and between the same non-invasively recorded waves (green line). ICU patient with impaired autoregulation, 1-hour continuous monitoring, spontaneous variations of the autoregulation state

KEY RESEARCH ACCOMPLISHMENTS

1.0. Approved statement of work: non-invasive ICP measurement through the human eye.

1.1. Develop ultrasonic signal transmitting / receiving technology for space resolution and eye artery blood flow velocity dynamic measurement resolution.
Accomplishment: a prototype battery powered device has been designed, manufactured and successfully tested (photo 1).

1.2. Develop and test the processing technology needed for measured eye artery blood velocities dynamic data comparison in two segments of the eye artery and the identification of flow balance in the two segments.
Accomplishment: standard Gosling pulsatility indexes were applied for preliminary balance identification in ICU conditions. Non-invasive absolute ICP measurements were performed on ICU patients (traumatic brain injuries) simultaneously with invasive ICP measurements following Clinical Research Protocol No. 9912 4006, AIBS No. 990135, HSSRB Log No. A – 9676. The clinical study is continuing and will be completed when 52 invasive and non-invasive monitoring one-hour periods are performed.
A non-standard balance index has been proposed and tested applying computer modeling. This new, more sensitive index for balance is based on the blood flow wave amplitude spectral analysis. New software for automatic balance indication applying the new balance index is under creation.

1.3. Develop the technique for application of pressure to the human eye together with its measurement and measurement of the eye artery blood flow velocity in two depths.
Accomplishment: a prototype has been developed and successfully preliminarily tested in ICU (photo 1).

1.4. Develop and construct breadboards and a prototype unit to prove the technology.
Accomplishment: the prototype has been developed and successfully preliminarily tested in ICU (photo 1).

1.5. Perform clinical evaluation of the prototype.
Accomplishment: the prototype has been evaluated in ICU. Invasive and non-invasive measurement data of absolute ICP are shown in Fig. 22 – Fig. 25.

2.0. Approved statement of work: non-invasive ICP / volume real - time monitoring:

2.1. To develop and test the technology for real-time elimination of the ultrasonic signals delay in external tissues and skull inside the acoustic path.
Accomplishment: the technology has been developed and successfully clinically tested in ICU.

2.2. To develop the received signals digital processing technologies for elimination of the possible Doppler shift of ultrasonic signals propagating through the parenchymal acoustic path.
Accomplishment: the technology has been developed and successfully clinically tested in ICU.

2.3. To develop and test the ultrasonic transducer of a suitable size, to monitor the pressure for battlefield and ICU applications.

Accomplishment: two types of smaller transducers have been designed, manufactured and preliminarily tested.

2.4. Develop and construct the breadboard and prototype unit to prove the technology of non-invasive ICP / volume and intracranial blood flow autoregulation state monitoring.
Accomplishment: the breadboards and prototype unit have been developed and manufactured. The prototype has been successfully clinically preliminarily tested in ICU following Clinical Research Protocol No. 9912 4006, AIBS No. 990135, HSSRB Log No. A – 9676. 28 simultaneous invasive and non-invasive ICP monitoring sessions have been performed in ICU on patients with traumatic brain injuries. 22 sessions of cerebrovascular autoregulation continuous monitoring have been performed on ICU patients. The clinical study is continuing and will be completed during the second year of this work when 52 invasive and non-invasive monitoring periods are performed for simultaneous invasive and non-invasive ICP and continuous autoregulation state monitoring and when statistical significance of clinical data will be achieved.

Resume: All the approved statements of the work for the first year of this study have been successfully accomplished.

REPORTABLE OUTCOMES

The key research accomplishments were orally presented by Dr. A. Ragauskas at the conference ATACCC 2001 (Fort Walton Beach, September, 2001). Also the poster was presented there. The abstract of presentation is attached as an appendice to this report.

CONCLUSIONS

1. A prototype battery powered device for non-invasive absolute ICP measurement through the human eye has been designed, manufactured and successfully tested. Standard Gosling pulsatility indexes were applied for preliminary extracranial and intracranial eye artery blood flow balance identification in ICU conditions. Non-invasive absolute ICP measurements were performed on ICU patients (traumatic brain injuries) simultaneously with invasive ICP measurements following Clinical Research Protocol No. 9912 4006, AIBS No. 990135, HSSRB Log No. A – 9676. The clinical study is continuing and will be completed when 52 invasive and non-invasive monitoring one-hour periods are performed. A non-standard balance index has been proposed and tested applying computer modeling. This new index is more sensitive for balance and is based on the blood flow wave amplitude spectral analysis. New software for automatic balance indication applying the new balance index is under creation.

2. The preliminary clinical results show that the prototype two-depth TCD device for absolute ICP measurement can be used in ICU environment. Our limited clinical experience (25 measurements, 3 patients) of the absolute ICP measurement below the critical level of ICP = 25.0 mmHg applying PI as a balance indicator shows that the systematic error of non-invasive absolute ICP is always positive and does not exceed 20%...25% of the invasively measured mean absolute ICP value.

3. To decrease the errors of non-invasive absolute ICP measurement it is necessary:
- to develop an extracranial pressure chamber applying the latex film as thin as possible in order to minimize the extracranial pressure gradient;
- to develop the rigid part of the extracranial pressure chamber also in order to minimize the extracranial pressure gradient during the measurements;
- to develop a software for two-depth TCD measurement data computer analysis (PC connected with the two-depth TCD prototype device) and for the indication of intracranial and extracranial pressure balance in ICU environment;
- to develop a software for non-standard index calculation to obtain a more sensitive disbalance of blood flow in the eye artery;
- to perform absolute ICP measurements in ICU applying the indexes mentioned;
- to a collect statistically significant number of clinical simultaneous invasive and non-invasive absolute ICP measurement data following Clinical Research Protocol No. 9912 4006, AIBS No. 990135, HSSRB Log No. A – 9676 by September 2002,
- to perform experimental evaluation of the potential accuracy of non-invasive absolute ICP meter in the situation when the TCD signal to noise ration is the best possible. In order to perform this experiment the standard echo-contrast agents (e.g., Levovist, Schering, Germany) need to be used during two-depth TCD measurements of the eye artery blood flow.

4. Vittamed time-of-flight technology has been developed applying real-time elimination of the ultrasonic signals delay in extracranial tissues and skull, which are inside the transcranial acoustic path. The digital signal processing technologies have been developed for the elimination of a possible Doppler shift of ultrasonic signals propagating through the parenchymal acoustic path.

5. A prototype time-of-flight device for cerebrovascular autoregulation state non-invasive monitoring has been designed and successfully tested in ICU following Clinical Research Protocol No. 9912 4006, AIBS No. 990135, HSSRB Log No. A – 9676. 28 simultaneous invasive and non-invasive ICP monitoring sessions were performed in ICU on patients with traumatic brain injuries. 22 sessions of cerebrovascular autoregulation continuous monitoring

were performed on ICU patients. The clinical study is continuing and will be completed during the second year of this work when 52 invasive and non-invasive monitoring periods are performed for simultaneous invasive and non-invasive ICP and continuous autoregulation state monitoring and when statistical significance of clinical data is achieved.

6. The achieved difference between absolute invasive and non-invasive ICP data during simultaneous invasive and non-invasive clinical monitoring of the patients with traumatic brain injury was within the error corridor of +/-2.0 mmHg. The errors of both devices (Camino and Vittamed) are within this error corridor because the uncertainty of Camino data is also +/-2.0 mmHg. In this case calibration of Vittamed monitor was performed using Camino monitor. A linear conversion of non-invasively measured ultrasound speed data into absolute ICP values has been used. This result is the evidence of an effective compensation of extracranial tissue blood flow phenomena and also of an effective compensation of the possible Doppler shift of ultrasonic signal propagating along the transintracranial acoustic path.

7. Simultaneous invasive and non-invasive recording of slow ICP and slow intracranial parenchymal blood volume waves show a high cross - correlation between invasively and non-invasively measured slow waves. The achieved highest cross – correlation values were $R_{C/V}$ = 0.92 ... 0.94 during one-hour continuous monitoring session. In the worst case of an unstable patient $R_{C/V}$ was more than 0.7 during 88% of monitoring time and $R_{C/V}$ was more than 0.8 during 78% of monitoring time. These results are a clinical evidence that invasive slow wave monitoring can be replaced by non-invasive slow wave monitoring for continuous estimation of cerebrovascular autoregulation state.

8. It is shown experimentally that an optimal adjustment of SaO2 and ETCO2 in the case of impaired cerebrovascular autoregulation can "switch-on" in some cases the intact cerebrovascular autoregulation. Both invasive and non-invasive autoregulation monitoring techniques clearly show the same dynamics of transient process of intact autoregulation restoration in the case of intact autoregulation "switching-on".

9. All the approved statements of the work for the first year of this study have been successfully accomplished.

4.REFERENCES

1.0. NON-INVASIVE ICP MEASUREMENT THROUGH THE HUMAN EYE

1. Part B: Description of Scientific/Technological Objectives and Work Plan. Proposal for Research and Technological Development (RTD) Support for the Brain-IT Project. Glasgow RTD FF5 Proposal 11.29.1999.
2. **Ragauskas A., Daubaris G.** A method and apparatus for non-invasively deriving and indicating of dynamic characteristics of the human and animal intracranial media. US Patent Nr. 5388583, Priority from Sept, 1993, published 1995; Int. Patent Application PCT/IB94/00293, Intern. Publication WO95/06435, 1995; European Patent 0717606, 1999.
3. **Ragauskas A. Daubaris G., Džiugys A.** Method and apparatus for determining the pressure inside the brain. US Patent Nr. 5951477, 14 September 1999.
4. Ragauskas A., Petkus V., Jurkonis R. **Simulation of ultrasound pulse propagation through human cranium. J. IFMBE "Medical & Biolog. Engineering & Computing", 1999, Vol. 37, Suppl. 1, p. 426- 427.**
5. **Petkus V., Ragauskas A.** Mathematical modeling of ultrasonic signal transmission through the human skull and brain. Measurements, 2000, No. 1(13), p. 12 - 19 (in Lithuanian).
6. **Allocca J. A.** Method and apparatus for noninvasive monitoring of intracranial pressure. US Patent Nr. 4204547, 27 May 1980.
7. **Rosenfeld, John G., Watts, Clark, York, Donald H.** Method and apparatus for intracranial pressure estimation: US Patent Nr. 4564022, 14 January 1986.
8. **Kageyama N., Sakuma N.** Apparatus for recording intracranial pressure. US Patent Nr. 4971061, 20 November 1990.
9. **Kageyama N., Sakuma N.** Apparatus for measuring intracranial pressure. US Patent Nr. 4984567, 15 January 1991.
10. **Mick E. C.** Method and apparatus for the for measurement intracranial pressure. US Patent Nr. 5117835, 2 June 1992.
11. **Yost W. T., Cantrell Jr. J. H.** Non-invasive method and apparatus for monitoring intracranial pressure and pressure volume index in humans: US Patent 5617873, 8 April 1997.
12. **Paulat K.** Method and device for measurement the intracranial pressure in the skull of a test subject. WO 97/30630, 20 February 1997.
13. **Bridger K., Cooke A. V., Crowne F. J., Kuhn P. M., Lutian J. J., Passaro E. J., Sewell J. M.** Apparatus and method for measurement of intracranial pressure with lower frequencies of acoustic signal. US Patent 5919144, 6 July 1999.
14. **Alperin N.** Method for measurement intracranial pressure. US Patent 5993398, 30 November 1999.
15. **Denninghoff K. R.** Oxymetric tonometer with intracranial pressure monitoring capability. WO 99/65387, 23 December 1999.
16. **Madsen J. R., Taylor G. A.** Non-invasive in vivo pressure measurement. US Patent 6086533, 11 July 2000.
17. **Borchert M. S., Lambert J. L.** Non-invasive method for measuring cerebral spinal fluid pressure. US Patent 6129682, 10 October 2000.
18. **Sinha D. N.** Method for noninvasive intracranial pressure measurement. US Patent 6117089, 12 September 2000.
19. **Michaeli D.** Noninvasive monitoring of intracranial pressure. WO 00/68467, 16 November 2000.
20. **Petkus V., Ragauskas A., Jurkonis R.** Theoretical model of intracranial media ultrasonic attenuation measurement method. Ultrasound, 2000, No 1 (34), p. 13-19.

21. **Ragauskas A., Daubaris G., Rocka S., Petkus V.** Innovative technologies of head injury physiological monitoring. Ultrasound, 2000, No 4 (37), p. 51-57.

2.0. NON-INVASIVE ICP / VOLUME REAL - TIME MONITORING

1. **Aaslid R, Lindegaard KF, Sorteberg W, Nornes H** (1989). Cerebral autoregulation dynamics in humans. Stroke 20, 45-52

2. **Aaslid R, Newell DW, Stooss R, Sorteberg W, LIndegaard KF** (1991). Assessment of Cerebral Autoregulation Dynamics From Simultaneous Arterial and Venous transcranial Doppler Recording in Humans. Stroke 22, 1148-1154

3. **Akselrod S, Gordon D, Madwed JB, Snidman N, Shannon C, Cohen RJ** (1985). Hemodynamic regulation: investigation by spectral analysis. Am J Physiol 249, H867-H875

4. **Allen KL, Bunt EA** (1989). Slow oscillation of compliance and pressure rate in the naturally closed cranio-spinal system. ICP VII. Eds. Hoff JT, Betz AL. Springer-Verlag Berlin Heidelberg, 251-254

5. **Andersson B, Kenney RA, Neil E** (1950). The role of the chemoreceptors of the carotid and aortic regions in the production of the Mayer waves. Acta Physiol Scand 20, 203-220

6. **Auer L, Gallhofer B** (1981). Rhythmic activity of cat pial vessels in vivo. Eur Neurol 20, 448-468

7. **Auer LM, Sayama I** (1983). Intracranial pressure oscillations (B-waves) caused by oscillations in cerebrovascular volume. Acta Neurochir 68, 93-100

8. **Baharav A, Kotagal S, Gibbons V, Rubin BK, Pratt G, Karin J, Akselrod S** (1995). Fluctuations in autonomic nervous activity during sleep displayed by power spectrum analysis of heart rate variability. Neurology 45, 1183-1187

9. **Bech RA, Juhler M, Waldemar G, Klinken L, Gjerris F** (1997). Frontal brain and leptomeningeal biopsy specimens correlated with cerebrospinal fluid outflow resistance and B-wave activity in patients suspected of normal-pressure hydrocephalus. Neurosurgery 40, 497-502

10. **Blaber AP, Bondar RL, Stein F, Dunphy PT, Moradshahi P, Kassam MS, Freeman R** (1992). Transfer function analysis of cerebral autoregulation dynamics in autonomic failure patients. Stroke 28, 1686-1692

11. **Borgesen SE, Gjerris F** (1982). The predictive value of conductance to outflow of CSF in normal pressure hydrocephalus. Brain 105, 65-86

12. **Bouma GJ, Muizelaar JP, Bandoh K, Marmarou A** (1992). Blood pressure and intracranial pressure-volume dynamics in severe head injury: relationship with cerebral blood flow. J Neurosurg 77, 15-19

13. Brain Trauma Foundation, American Association of Neurological Surgeons, joint Section on neurotrauma and critical care. Intracranial pressure treatment threshold. In Guidelines for the management of severe head injury. Park Ridge: BTF, AANS, chap 6

14. **Brock M, Tamburus WM, Telles Ribeiro CR, Dietz H** (1978). Circadian occurrence of pathologic cerebrospinal fluid pressure waves in patients with brain tumors. Advances in neurosurgery 5, Springer Berlin, 188-193

15. **Calbucci F, Dallolio W, Benerecetti E, Dorizzi A, Munari C** (1980). Polygraphic study of CSF pressure waves during coma. ICP IV. Eds. Shulman K, Marmarou A, Miller JD, Becker DP, Hochwald GM, Brock M. Springer-Verlag Berlin Heidelberg New York. 229-234

16. **Carrol GC** (1990). Fourth-order blood pressure waves. JAMA 263, 856-857

17. **Castel JP, Dartigues JF**, Vandendriessche (1980). Pathological intracranial pressure waves in Arnold Chiari malformations. ICP IV. Eds. Shulman K, Marmarou A, Miller JD, Becker DP, Hochwald GM, Brock M. Springer-Verlag Berlin Heidelberg New York. 569-574

18. **Chawla JC, Hulme A, Cooper R** (1974). Intracranial pressure in patients with dementia and communicating hydrocephalus. J Neurosurg 40, 376-380
19. **Cooper R, Hulme A** (1966). Intracranial pressure and related phenomena during sleep. J Neurol Neurosurg Psychia 29, 564-570
20. **Czosnyka M, Pickard J, Whitehouse H, Piechnik S** (1992). The hyperaemic response to a transient reduction in cerebral perfusion pressure. Acta Neurochir 115, 90-97
21. **Czosnika M, Smielewski P, Kirkpatrick P, Menon DK, Pickard JD** (1996). Monitoring of cerebral autoregulation in head-injured patients. Stroke 27, 1829-1834
22. **Czosnika M, Smielewski P, Kirkpatrick P, Laing RJ, Menon D, Pickard JD** (1997). Continuous assessment of the cerebral vasomotor reactivity in head injury. Neurosurgery 41, 11-19
23. **Czosnyka M, Smielewski P, Piechnik S, Schmidt E, Al-Rawi PG, Kirkpatrick PJ, Pickard JD** (1999). Hemodynamic characterization of intracranial pressure plateau waves in head-injured patients. J Neurosurg 91, 11-19 **(also private communication with Dr M Czosnyka)**.
24. **Dawson SL, Blake MJ, Panerai RB, Potter JF** (2000). Dynamic but not static cerebral autoregulation is impaired in acute ischaemic stroke. Cerebrovasc Dis 10, 126-132 **(also private communication with Dr RB Panerai).**
25. **Diehl RR, Linden D, Lücke D, Berlit P** (1995). Phase relationship between cerebral blood flow velocity and blood pressure. A clinical test of autoregulation. Stroke 26, 1801-1804
26. **Dirnagl U, Garner C, Haberl R, Mautner D, Schmiedek P** (1989). Correlation between B-waves and intracranial pressure – volume relationships. ICP VII. Eds. Hoff JT, Betz AL. Springer-Verlag Berlin Heidelberg, 213-216
27. **Dora E, Kovach A** (1981). Metabolic and vascular volume oscillations in the cat brain cortex. Acta Acad Sci Hung 57, 261-275
28. **Droste DW, Krauss JK, Berger W, Schuler E, Brown MM** (1994). Rhythmic oscillations with a wavelength of 0.5-2 min in transcranial Doppler recordings. Acta Neurol Scand 90, 99-104
29. **Droste DW, Krauss JK** (1999). Intracranial pressure B-waves precede corresponding arterial blood pressure oscillations in patients with suspected normal pressure hydrocephalus. Neurological Research 21, 627-630
30. **Einhäupl KM, Garner C, Dirnagl U, Schmieder G, Schmiedek P, Kufner G, Rieder J** (1986). Oscillations of ICP related to cardiovascular parameters. ICP VI, Eds. Miller JD, Teasdale GM, Rowan JO, Galbraith SL, Mendelow AD. Springer-Verlag Berlin Heidelberg, 290-297
31. **Enevoldsen EM, Jensen FT** (1978). Autoregulation and CO2 responses of cerebral blood flow in patients with acute severe head injury. J Neurosurg 48, 689-703
32. **Furuse M, Kuchiwaki H, Nakaya T, Toyama K, Teraoka M, Hasuo M, Ikeyama A, Kagema N** (1980). Relationship between rapid ICP variation, respiratory pattern and wakefulness in neurological patients. ICP IV. Eds. Shulman K, Marmarou A, Miller JD, Becker DP, Hochwald GM, Brock M. Springer-Verlag Berlin Heidelberg New York. 584-587
33. **Giller CA** (1990). The frequency-dependant behaviour of cerebral autoregulation. Neurosurgery 3, 362-368
34. **Giller CA** (1991). A bedside test for cerebral autoregulation using transcranial Doppler ultrasound. Acta Neurochir 108, 7-14
35. **Godersky JC, Graff-Radford NR** (1991). Evaluation of pressure monitoring and CSF conductance in NPH. ICP VIII. Eds. Avezaat CJJ, Eijndhoven JHM, Maas AIR, Tans JTT. Springer Verlag Berlin Heidelberg. 811-815
36. **Guyton AC** (1996). Précis de physiologie médicale, Régulation nerveuse de la circulation et contrôle rapide de la pression artérielle (chap 18, 194-204). A Lockhart (translation): textbook of medical physiology (1991) 8th edition. Eds. Piccin Nuova Libraria, Padoue (Italia)

37. **Gündüz G, Viernstein LW** (1979). Intracranial pressure in the normal monkey while awake and asleep. J Neurosurg 51, 206-210
38. **Hara K, Nakatami S, Osaki K, Mogami A** (1989). A minicomputer system for analysis and display of ICP data. ICP VII. Eds. Hoff JT, Betz AL Springer-Verlag Berlin Heidelberg. 132-134
39. **Harper AM** (1966). Autoregulation of cerebral blood flow: influence of arterial blood pressure on the blood flow through the cerebral cortex. J Neurol Neurosurg Psychiat 29, 398-403
40. **Hayashi M, Marukawa S, Fuji H, Kitano T, Kobayashi H, Yamamoto S** (1977). Intracranial hypertension in patients with ruptured aneurysm. J Neurosurg 46, 584-590
41. **Hayashi M, Kobayashi H, Fuji H, Yamamoto S** (1982). Ventricular size and isotope cisternography in patients with acute transient rises of intracranial pressure (plateau waves). J Neurosurg 57, 797-803
42. **Hayashi M, Kobayashi H, Handa Y, Kawano H, Ishii H** (1986). CSF fluid dynamics in patients with plateau waves. ICP VI Eds. JD Miller GM Teasdale JO Rowan SL Galbraith AD Mendelow (Springer Berlin Heidelberg) 305-309
43. **Hayashi M, Handa Y, Kobayashi H, Kawano H, Ishii H, Hirose S** (1991). Plateau-wave phenomenon (I) correlation between the appearance of plateau waves and CSF circulation in patients with intracranial hypertension. Brain 114, 2681-2691
44. **Higashi S, Yamamoto S, Hashimoto M, Fuji H, Ito H, Kogure Y, Tokuda K** (1989). The role of vasomotor centre and the adrenergic pathway in B-waves. ICP VII. Eds. Hoff JT, Betz AL Springer-Verlag Berlin Heidelberg. 220-240
45. **Hundley WG, Renaldo GJ, Levasseur JE, Kontos HA** (1988). Vasomotion in cerebral microcirculation of awake rabbits. Heart Circ Physiol 23, H67-H71
46. **Hyndman BW, Kitney RI, Sayers BM** (1971). Spontaneous rhythms in physiological control systems. Nature 223, 339-341
47. **Janny P** (1950). La pression intra-crânienne chez l'homme. Méthode d'enregistrement – Etude de ses variations et de ses rapports avec les signes cliniques et ophtalmologiques. Thesis, Paris
48. **Janny P, Colnet G, Veyre A, Chazal J, Barreto LC** (1981). Hydrocephalie à pression normale. Etude pré- et postopératoire de 56 cas. Neurochirurgie 27, 89-96
49. **Jones SC, Williams JL, Shea M, Easley KA, Datong W** (1995). Cortical blood flow cycling: anesthesia and arterial blood pressure. Am J Physiol 268, H569-H575
50. **Kinoshita K, Katayama Y, Hirayama T, Maejima S, Tsubokaw T** (1994). Changes in jugular oxygen saturation associated with intracranial pressure. ICP IX. Eds. Nagai H, Kamiya K, Ishii S. Springer-Verlag Berlin Heidelberg New York London Paris Tokyo Hong Kong Barcelona Budapest. 514-515
51. **Kirkeby OJ, Rise IR, Nordsletten L, Skjeldal S, RisØe C** (1995). Cardiovascular response to blood loss during high intracranial pressure. J Neurosurg 83, 1067-1069
52. **Kogure Y, Fujii H, Higashi S, Hashimoto K, Tokuda K, Ito H, Yamamoto S** (1989). Electroencephalographic changes during plateau-waves – plateau waves induced by electrical stimulation of the brain stem. ICP VII. Eds. Hoff JT, Betz AL Springer-Verlag Berlin Heidelberg. 235-237
53. **Kontos HA, Wei EP, Navari RM, Levasseur JE, Rosenblum WI, Patterson JL** (1978). Responses of cerebral arteries and arterioles to acute hypotension and hypertension. Am J Physiol 234, H371-H383
54. **Krauss JK, Droste DW, Bohus M, Regel JP, Scheremet R, Riemann D, Seeger W** (1995). The relation of intracranial pressure B-waves to different sleep stages in patients with suspected normal pressure hydrocephalus. Acta Neuro 136, 195-203
55. **Lamas L, Lobato RD, Esparza J** (1980). Long-term intraventricular pressure measurement in chronic communicating hydrocephalus. ICP IV. Eds. Shulman K, Marmarou A,

Miller JD, Becker DP, Hochwald GM, Brock M. Springer-Verlag Berlin Heidelberg New York. 505-510
56. **Lang EW, Randall MC** (1994). Intracranial pressure. Monitoring and management. Neurosurg Clinics North America 4, 573-605
57. **Lange RL, Hecht HH** (1962). The mechanism of Cheyne-Stokes respiration. J Clin Invest 41, 42-52
58. **Larsen FS, Olsen KS, Hansen BA, Paulson OB, Knudsen GM** (1994). Transcranial Doppler is valid for determination of the lower limit of cerebral blood flow autoregulation. Stroke 25, 1985-1988
59. **Lemaire JJ, Boire JY, Chazal J, Irthum B** (1994). A computer software for frequential analysis of slow intracranial pressure waves. Comput Methods Programs Biomed, 42, 1-14
60. **Lemaire JJ, Irthum B, Chazal J, Boire JY** (1994). Statistical analysis of ICP and frequential analysis of slow waves during the course of subarachnoid haemorrhage following arterial aneurysm rupture: effects of vasospasm. ICP IX. Eds. Nagai H, Kamiya K, Ishii S. Springer-Verlag Berlin Heidelberg New York London Paris Tokyo Hong Kong Barcelona Budapest. 184-188
61. **Lemaire JJ, Chazal J, Gutknecht JL, Picard P, Irthum B, Boire JY** (1994). Effects of acute compliance fluctuation on slow ICP waves: frequential aspects. ICP IX. Eds. Nagai H, Kamiya K, Ishii S. Springer-Verlag Berlin Heidelberg New York London Paris Tokyo Hong Kong Barcelona Budapest. 498-501
62. **Lemaire JJ, Burlat JF, Khalil T, Chabane A, Irthum B, Chazal J** (1998). Computer software for frequential monitoring of intracranial pressure (and related signals) slow waves. Intracranial Pressure and Neuromonitoring brain Injury. Eds. Marmarou A, Bullock R, Avezaat C, Baethmann A, Becker D, Brock M, Hoff J, Nagai H, Reulen HJ, Teasdale G. Acta Neurochirugica [suppl] 71: 388
63. **Lemaire JJ, Khalil T, Cervenansky F, Boire JY, Sinardet D, Schmidt E, Fischer-Lokou D, Irthum B, Chazal J, Bonnard-Gougeon M** (1998). Nouvelle méthode d'étude clinique de la vasomotricité cérébrale: approche de l'autorégulation dynamique ?Abstract XX^{èmes} journées de l'Association de Neuro-anesthésie réanimation de langue Française. Paris, Sorbonne 19-20 novembre 1998 **(also private communication with Prof. JJ Lemaire).**
64. **Littler WA, West MJ, Honour AJ, Sleight** (1978). The variability of arterial pressure. American Heart J 95, 180-186
65. **Lorenz R** (1976). The Cushing Response. ICP III. Eds. Beks JWF, Bosch DA, Brock M Springer-Verlag Berlin Heidelberg New York. 270-278
66. **Lundar T, Lindegaard KF, Nornes H** (1989). Continuous monitoring of middle cerebral arterial blood velocity and cerebral perfusion pressure. ICP VII. Eds. Hoff JT, Betz AL. Springer-Verlag Berlin Heidelberg, 101-105
67. **Lundberg N** (1960). Continuous recording and control of ventricular fluid pressure in neurosurgical practice. Acta Psychiat Scand, 36, suppl 149
68. **MacGillicuddy JE, Kindt GW, Raisis JE, Miller CA** (1978). The relation of cerebral ischemia, hypoxia, and hypercarbia to the Cushing response. J Neurosurg 48, 730-740
69. **MacKenzie ET, McGeorges AP, Graham DI, Fitch W, Edvinsson L, Harper AM** (1977). Breakthrough of cerebral autoregulation and the sympathetic nervous system. Acta Neurol Scand 56, 48-49
70. **Maeda M, Miyazaki M** (1998). Control of ICP and the cerebrovascular bed by the cholinergic basal forebrain. Acta Neurochir [suppl] 71: 293-296
71. **Maeda M, Takashashi K, Miyazaki M, Ishii S** (1986). The role of central monamine system and the cholinoceptive pontine area on the oscillation of ICP "pressure waves". ICP VI. Eds. Miller JD, Teasdale GM, Rowan JO, Galbraith SL, Mendelow AD Springer-Verlag Berlin Heidelberg. 151-155
72. **Maeda M, Tanaka K, Nishimur S, Matsuura S** (1986). Pressure wave-like changes in

ICP produced by electrical stimulation of the brainstem, hypothalamus and cerebral cortex in cats. ICP VI. Eds. Miller JD, Teasdale GM, Rowan JO, Galbraith SL, Mendelow AD Springer-Verlag Berlin Heidelberg. 156-160
73. **Maeda M, Matsuura S** (1989). Increase in ICP produced by electrical stimulation of the brain stem reticular formation in cats with spinal vagotomy. ICP VII. Eds. Hoff JT, Betz AL Springer-Verlag Berlin Heidelberg. 292-294
74. **Maeda M, Miyazaki M, Ishii S** (1989). The roles of the mutual interaction between the locus coeruleus complex and the chorioceptive pontine area in the plateau wave. ICP VII. Eds. Hoff JT, Betz AL Springer-Verlag Berlin Heidelberg. 228-231
75. **Maeda M, Miyazaki M, Ishii S** (1991). Control of ICP by the medullary reticular formation. ICP VIII. Eds. Avezaat CJJ, Eijndhoven JHM, Maas AIR, Tans JTT. Springer Verlag Berlin Heidelberg. 207-213
76. **Maeda M, Miyazaki M** (1998). Control of ICP and the cerebrovascular bed by the cholinergic basal forebrain. Acta Neurochir [Suppl] 71, 293-296
77. **Maira G, Rossi GF, Vignati A** (1975). Intracranial pressure and pathogenesis of "normotensive" hydrocephalus. ICP II Eds. N Lundberg M Brock Springer Verlag Berlin Heidelberg NewYork, 128-132
78. **Mancia G, Ferrari A, Gregorini L, Parati G, Pomidossi G, Bertinieri G, Grassi G, Marco Di Rienzo, Pedotti A, Zanchetti A** (1983). Blood pressure and heart rate variabilities in normotensive and hypertensive human beings. Cir Res 53, 96-104
79. **Matsuda M, Yoneda S, Handa H, Gotoh H** (1979). Cerebral hemodynamic changes during plateau waves in brain-tumor patients. J Neurosurg 50, 483-488
80. **Mautner-Huppert D, Haberl RL, Dirnagl U, Villringer A, Schmiedek P, Einhäupl K** (1989). B-Waves in healthy persons. Neurological Research 11, 194-196
81. **Mayevsky A, Ziv I** (1991). Oscillations of cortical oxidative metabolism and microcirculation in the ischemic brain. Neurol Rev 13, 39-47
82. **Miller JD** (1987). ICP monitoring - Current status and future directions. Acta Neurochir 85, 80-86
83. **Munari C, Calbucci F** (1979). Corrélations entre pression intracrânienne et EEG au cours des comas traumatiques. Rev EEG Neurophysiol 9, 185-193
84. **Muizelaar JP, Ward JD, Marmarou A, Newlon PG, Wachi A** (1989). Cerebral blood flow and metabolism in severely head-injured children. J Neurosurg 71, 72-76
85. **Newell DW, Aaslid R, Stooss R, Reulen HJ** (1992). The relationship of blood flow fluctuations to intracranial pressure B waves. J Neurosurg 76, 415-421
86. **Newell DW, Aaslid R, Stooss R, Reulen HJ** (1993). Spontaneous fluctuations in cerebral blood flow as a cause of B waves. ICP VIII. Eds. Avezaat CJJ, Van Eijdhoven JHM, Maas AIR, Tans JTT. Springer-Verlag Berlin Heidelberg New York London Paris Tokyo Hong Kong Barcelona Budapest. 424-428
87. **Newell DW, Weber JP, Watson R, Aaslid R, Winn HR** (1996). Effect of transient moderate hyperventilation on dynamic cerebral autoregulation after sever head injury. Neurosurgery 39, 35-44
88. **Newell DW, Aaslid R, Stoos RW, Seiler RW, Reulen HJ** (1997). Evaluation of hemodynamic responses in head injury patients with transcranial Doppler monitoring. Acta Neurochirurgica 139, 804-817
89. **Nornes H, Magnaes B, Aaslid R** (1972). Observations in intracranial pressure plateau waves. Intracranial pressure. Eds. Brock M and Dietz H (Springer-Verlag Berlin Heidelberg New York), 421-426 **(also private communication with Dr. R Aaslid)**
90. **Novak V, Novak P, Spies JM, Low PA** (1997). Autoregulation of cerebral blood flow in orthostatic hypotension. Stroke 1998, 104-111
91. **Onitsuka T, Takeda Y, Miki T, Haraoka J, Ito Y** (1994). Regional cortical blood flow in appearance of pressure wave. A clinical study in patients with B waves. ICP IX. Eds. Nagai H,

Kamiya K, Ishii S. Springer-Verlag Berlin Heidelberg New York London Paris Tokyo Hong Kong Barcelona Budapest. 204-207
92. **Oppenheimer S** (1993). The anatomy and physiology of cortical mechanisms of cardiac control. Stroke 24 [suppl I], I-3 – I-5
93. **Passatore M, Deriu F, Roatta S, Grassi C, Micieli G** (1995). Effects of cervical sympathetic nerve stimulation on the cerebral microcirculation: possible clinical implications. Acta Neurobiol Exp 56, 117-127
94. **Panerai RB, Kelsall WR, Rennie JM, Evans DH** (1995). Cerebral autoregulation dynamics in premature new-borns. Stroke 26, 74-80
95. **Panerai RB, White RP, Markus HS, Evans DH** (1998). Grading of cerebral dynamic autoregulation from spontaneous fluctuations in arterial blood pressure. Stroke 29, 2341-2346
96. **Pickard JD, Teasdale G, Matheson M, Lindsay K, Galbraigth S, Wyper D, Macpherson P** (1980). Intraventricular pressure waves – The best predictive test for shunting in normal pressure hydrocephalus. ICP IV. Eds. Shulman K, Marmarou A, Miller JD, Becker DP, Hochwald GM, Brock M. Springer-Verlag Berlin Heidelberg New York. 498-500
97. **Pierre-Kahn A, Gasbersek V, Hirsch JC** (1974). Phase paradoxale du sommeil et pression intracrânienne au cours de l'hydrocéphalie stabilisée. Rev EEG Neurophysio 5, 5-9
98. **Piper IR, Chan KH, Whittle IR, Miller JD** (1993). An experimental study of cerebrovascular resistance, pressure transmission, and craniospinal compliance. Neurosurgery 32, 805-816 **(also private communication with Dr. I Piper)**
99. **Preiss G, Polosa C** (1974). Patterns of sympathetic neurone activity associated with Mayer waves. Am J Physiol 226, 724-729
100. **Price DJ, Saxena A, Czosnyka M** (1998). The relationship of vasogenic waves to ICP and cerebral perfusion pressure in head injuries patients. Acta Neurochir [suppl] 71, 297-299
101. **Rafferty C, Teasdale GM, Bullock R, Fitch W, Farling P** (1991). Changes in jugular bulb oxygen saturation and associated changes in intracranial pressure. ICP VIII. Eds. CJJ Avezaat, JHM Eijndhoven, AIR Maas, JTT Tans (Springer Verlag Berlin Heidelberg New York London Paris Honk kong Barcelona Budapest), 418-423
102. **Raftopoulos C, Chaskis C, Delecluse F, Cantraine F, Bidaut L, Brotchi J** (1992). Morphological quantitative analysis of intracranial pressure waves in normal pressure hydrocephalus. Neurol Research 14, 389-396
103. **Reilly PL, Farrar JK, Miller JD** (1977). Vascular reactivity in the primate brain after cryogenic injury. J Neurol Neurosurg Psy 40, 1092-1101
104. **Risberg J, Lundberg N, Ingvar DH** (1969). Regional cerebral blood volume during acute transient rises of the intracranial pressure (plateau waves). J Neurosurg, 31, 303-310
105. **Robertson CS, Contant CF, Narayan RK, Grossman RG** (1991). Comparison of methods for ICP waveform analysis with intracranial hypertension in head-injured patients. ICP VIII. Eds. CJJ Avezaat, JHM Eijndhoven, AIR Maas, JTT Tans (Springer Verlag Berlin Heidelberg New York London Paris Honk kong Barcelona Budapest), 348-355
106. **Rosiello AP, McClearly EL, Cooper PR** (1989). Non-provocative assessment of intracranial volume – pressure relationships. ICP VII. Eds. JT Hoff, AL Betz (Springer Verlag Berlin Heidelberg), 260-262
107. **Rosner MJ, Becker DP** (1984). Origin and evolution of plateau waves, experimental observations and a theoretical model. J Neurosurg 60, 312-324
108. **Rosner MJ** (1991). Cyclic CSF pressure waves causally relate to systemic arterial blood pressure. ICP VIII. Eds. CJJ Avezaat, JHM Eijndhoven, AIR Maas, JTT Tans (Springer Verlag Berlin Heidelberg New York London Paris Honk kong Barcelona Budapest), 414-417
109. **Rougemont J, Barge M, Benabid AL** (1972). Correlative study of intracranial and systemic arterial pressures in neurosurgical patients. Intracranial pressure. Eds. Brock M and Dietz H (Springer-Verlag Berlin Heidelberg New York), 232-238
110. **Sirowski EB, Amcheslavski VG, Savin IA** (1994). Towards the mechanism of

spontaneous "B" and "plateau" waves. ICP IX. Eds. Nagai H, Kamiya K, Ishii S. Springer-Verlag Berlin Heidelberg New York London Paris Tokyo Hong Kong Barcelona Budapest. 490-492
111. **Smielewski P, Czosnika M, Kirkpatrick P, Pickard JD** (1997). Evaluation of the transient hyperemic response test in head injured patients. J Neurosurg 86, 773-778
112. **Steinmeier R, Bauhuf C, Hübner U, Dietrich Bauer R, Fahlbusch R, Laumer R, Bondar I** (1996). Slow rhythmic oscillations of blood pressure, intracranial pressure, microcirculation, and cerebral oxygenation. Stroke 27, 2236-2243
113. **Steiger HJ, Aaslid R, Stoos R, Seiler RW** (1994). Transcranial Doppler monitoring in head injury: relations between type of injury, flow velocities, vasoreactivity, and outcome. Neurosurgery 34, 79-86
114. **Strebel S, Lam AM, Matta BF, Newell DW** (1997). Impaired cerebral autoregulation after mild brain injury. Surg Neurol 47, 128-131
115. **Symon L and Dorsch NWC** (1975). Use of long-term intracranial pressure measurements to assess hydrocephalic patients prior to shunt surgery. J Neurosurg 42, 258-273
116. **Tanaka K, Nishimura S** (1989). The importance of outflow resistance of the shunt system for elimination of B-waves. ICP VII. Eds. JT Hoff, AL Betz (Springer Verlag Berlin Heidelberg), 368-373
117. **Teasdale GM, Graham DI** (1998). Craniocerebral trauma: protection and retrieval of the neuronal population after injury. Neurosurgery 43, 723-738
118. **Thorburn W** (1972). Recordings of applanating force at constant intraocular pressure. IV intraocular volume changes due to change in blood centent. Acta ophtalmo 50, 270-285
119. **Tiecks FP, Lam A, Aaslid R, Newell DW** (1995). Comparison of static and dynamic cerebral autoregulation measurement. Stroke 26, 1014-1019
120. **Tiecks FP, Lam AM, Matta BF, Strebel S, Douville C, Newell DW** (1995). Effects of the Valsalva manoeuvre on circulation in healthy adults. Stroke 26, 1386-1392
121. **Tsubokawa T, Katayama Y, Miyazaki S** (1989). Intracranial pressure in response to deep brain stimulation in traumatic prolonged coma patients. ICP VII. Eds. Hoff JT, Betz AL Springer-Verlag Berlin Heidelberg. 703-705
122. **Ursino M, Giammarco PD** (1991). A mathematical model of the relationship between cerebral blood volume and intracranial pressure changes: the generation of plateau waves. Ann Biomedical Engineer 19, 15-42 **(also private communication with Prof. M Ursino)**
123. **Venes JL** (1979). B Waves – A reflection of cardiorespiratory or cerebral nervous systems rhythm ? Child's brain 5, 352-360
124. **Vern BA, Schuette WH, Leheta B, Juel VC** (1988). Low frequency oscillations of cortical metabolism in waking and sleep. J Cereb Blood Flow Metab 8, 215-226
125. **Wayenberg JL, Hasaerts D, Franco P, Valente F, Massager N** (1995). Anterior fontanel pressure variations during sleep in healthy infants. Sleep 18, 223-228
126. **Yambe T, Nitta S-I, Naganuma S**, et al (1994). Fluctuations of the sympathetic nerve discharges in animals without natural heartbeat. Artif organs 18, 775-780
127. **Yokota A, Kohshi K, Kajiwara H** (1991). Intracranial pressure related to sleep. ICP VIII. Eds. CJJ Avezaat, JHM Eijndhoven, AIR Maas, JTT Tans (Springer Verlag Berlin Heidelberg New York London Paris Honk kong Barcelona Budapest), 522-524
128. **Sahuquillo J, Amoros S, Santos S, Poca MA, Valenzuela H, Baguena M, Garnacho A.** False autoregulation (pseudoregulation) in patients with severe head injury. Its importance in CPP management. Acta Neurochir (2000) [Suppl] 76: 485-490.
129. **Fountas KN, Robinson JS Jr., Ragauskas A, Daubaris G, Spakauskas B.** Innovative noninvasive technology for spinal cord canal compliance dynamics monitoring. Cerebrovasc Dis (2001); 11 (suppl 3):1-47, p. 44 **(also private communication with Prof. Robinson JS)**
130. **Fountas KN, Robinson JS Jr., Ragauskas A, Daubaris G.** Innovative noninvasive technologies for intracranial hydrodynamic measurements and diagnosing. 3rd International

hydrocephalus workshop, 17-20 May (2001), Kos, Greece, p. 76

APPENDICES

ATACCC 2001, Fort Walton Beach
(ABSTRACT OF ORAL PRESENTATION)

A. RAGAUSKAS

NON-INVASIVE MEASUREMENT OF INTRACRANIAL PRESSURE (ICP)

Objective: New ultrasonographic non-invasive ICP / Volume monitoring and ICP absolute value measurement methods were proposed in our previous works [1,2]. The objective of this paper is to present our clinical results of the assessment of non-invasive technology for cerebrovascular autoregulation monitoring and non-invasive ICP absolute value measurement in the intensive care unit (ICU).

Methods: Slow intracranial wave and ABP slow wave correlation methodology was used for cerebrovascular autoregulation monitoring. Non-invasive cerebrovascular slow wave monitor (Vittamed) has been used together with invasive ICP and ABP slow wave monitors in the ICU. Also ultrasonographic absolute ICP meter (Vittamed) was applied for periodic non-invasive measurements of ICU patients with traumatic brain injuries. All measurements were performed following Clinical Research Protocol of DoD Agreement DAMD 17-00-2-0065.

The non-invasively recorded slow volumetric intracranial waves were compared with invasively recorded slow ICP waves. Also continuous monitoring of the correlation factor R_I between invasively recorded ICP and ABP slow waves was performed simultaneously with non-invasively recorded correlation factor R_N between volumetric slow waves and ABP slow waves. The accuracy of absolute ICP non-invasive measurement was evaluated comparing non-invasive ICP data with simultaneously invasively measured ICP values.

Results: It has been shown experimentally that the correlation factor between invasively and non-invasively recorded slow ICP waves is not less than 0.71...0.93 during one hour monitoring periods (15 one hour ICU monitoring periods were analyzed). It has been shown an excellent agreement between non-invasive and invasive cerebrovascular autoregulation monitoring data.

The preliminary results of non-invasive ICP measurement method clinical assessment show that this is only method for non-invasive ICP measurement without the problem of individual calibration of system "patient – non-invasive ICP meter".

Conclusion: In this ongoing study it is shown at the first time that non-invasive ultrasonographic time-of-flight technology could be applied for continuous cerebrovascular autoregulation monitoring. It is shown that non-invasive absolute ICP meter (Vittamed) is only non-invasive ICP meter, which does not need an individual calibration of system "patient – non-invasive ICP meter".

1. Cerebrovasc Dis 1999;9 (suppl.2):31 and 46, also 2000;10 (suppl.1):34.
2. US Patents 5, 388, 583 and 5, 951, 477.

Research Protocol Involving Human Subjects

Project title: Non-Invasive Ultrasonic Diagnosing and Monitoring of Intracranial Pressure / Volume (Cooperative Agreement No. DAMD17 - 00 - 2 - 0065).

Responsible Investigator: Arminas Ragauskas, DSc., address: Saules 39-10, LT-3031 Kaunas, Lithuania, tel: +370 7 353807, fax: +370 7 736897, e-mail: telematics@tef.ktu.lt.

Location of Study: Neurosurgical Clinic of Kaunas Medical University, Eiveniu 2, LT-3005 Kaunas, Lithuania.

Site investigators: Algis Matukevicius, MD, Neurosurgeon,
Gediminas Daubaris, DSc., Clinical Scientist,
Rimantas Tarasevicius, Dr, Anaesthetist,
Vytenis Deltuva, MD, Neurosurgeon.

Time required to complete: 13 months.

Abbreviations:
ICP - intracranial pressure,
ABP - arterial blood pressure,
CPP - cerebral perfusion pressure,
TCD - transcranial Doppler,
TITF - transintracranial "time-of-flight",
MRI - magnetic resonance imaging,
ICU - intensive care unit.

1. Background

a. This protocol is part of a proposal to develop for battle field application and for the commercial market of medical diagnostic and monitoring two versions of noninvasive intracranial pressure (ICP) monitors based on ultrasound transmission and transduction. One system will use ultrasonic signal transmitting/receiving technology to measure eye artery blood flow velocities simultaneously within intracranial and extracranial segments of the eye artery, for noninvasive ICP absolute value measurement. The second system - an ICP monitor device using measures of signal attenuation and time-of-flight of the signal algorithms to assess ICP and intracranial volumes, for noninvasive ICP volume real-time monitoring. As opposed to other noninvasive intracranial pressure monitors under development, both of systems will provide absolute ICP values. This proposal describes devices that would replace current state of the art, invasive, ICP monitors.

b. The project will be directed by Al Petrikas, President of Vitta Corporation, Bethel, Connecticut. The research study will be conducted at the Neurosurgical Clinic of Kaunas Medical University with Arminas Ragauskas, DSc serving as the responsible investigator with a team of medical physicians serving as clinical sub-investigators.

c. More than 50 healthy volunteers and 32 intensive care unit coma subjects have been studied. In the case of healthy volunteers, it was shown that physiological changes of ICP and ICP waves as a result of cerebrospinal reactions to different challenges could be noninvasively measured with high resolution and accuracy. No adverse events caused by noninvasive technology were observed during the human study. The researchers have concluded from the

preliminary animal and human studies that acoustic properties of the microvascular parenchymal acoustic path can be detected and they represent intracranial blood volume changes and intracranial parenchyma tissue volume changes inside the acoustic path.

d. This project is a part of the Combat Causality Care program.

2. Research Design.

The protocol design of this experimental research project is presented in Section 5, "Protocol Design".

3. Research Objectives.

a. To conduct a clinical trial on intensive care unit coma patients with heads injuries and implanted existing standard invasive intracranial pressure (ICP) transducers connected to standard ICP monitors simultaneously with multidepth transcranial Doppler (TCD) measurements of the eye artery blood flow parameters in the intracranial and extracranial segments of that artery in the case of ICP equal to the external pressure applied to the eye.

b. To conduct a clinical trial on intensive care unit coma patients with head injuries and implanted existing standard invasive intracranial pressure (ICP) transducers connected to standard ICP monitors simultaneously with a new noninvasive ICP/volume monitor above the critical level ICP = 20...25 mmHg and below this level. To investigate the ability to apply a new noninvasive ICP/volume monitor for continuous monitoring of a head injured patient's cerebral blood flow autoregulation state.

4. Study population

Male and female subjects >18 years of age with traumatic brain injury.

We intend to study 10 patients with traumatic brain injury. Inclusion criteria: age >=18 years, brain injured patients monitored in intensive care unit who have invasive arterial and intracranial pressure monitoring. Indications for intracranial pressure monitoring are appropriate in patients with severe head injury with abnormal admission CT scan. Severe head injury is defined as a Glasgow Coma Scale Score of 3-8 after cardiopulmonary resuscitation. An abnormal CT scan of the head is one that reveals hematomas, contusions, edema, or compressed basal cisterns. ICP monitoring is appropriate in patients with severe head injury with a normal CT scan if two or more of the following features are noted at admission: age over 40 years, unilateral or bilateral motor posturing, systolic blood pressure less than 90 mmHg. ICP monitoring is not routinely indicated in patients with mild or moderate head injury (Guidelines for the Management of Severe Head Injury. Brain Trauma Foundation, USA, 1995). Following the Guidelines for the Management of Severe Head Injury the only comatose patients of ICU with implanted invasive ICP monitoring transducers will be involved into the study.
Post Sub-arachnoid haemorrhage patients monitored in intensive care unit who have invasive arterial and intracranial pressure monitoring. Exclusion criteria: patients with wounds, scars or a craniotomy overlying the optimal window for transintracranial ultrasonic measurement.

Declaration of a specific number of subjects for sample size

A goal of the experimental tests is evaluation of reliability of data obtained using new

noninvasive intracranial pressure measurement methods in comparison with the invasively measured data using intracranial pressure monitor.

The proposed noninvasive intracranial pressure measurement method does not influence the physiological state of patient. From the methodological point of view the object of investigation is not the individual patient but the physical parameter (intracranial pressure measured by two ways - invasively and noninvasively), reflecting the dynamics of physiological state of individual patient. Therefore, a separate patient can be repeatedly exploited to obtain the required statistics of sample data. The parameter values during measurement tests must cover the entire range of the parameter variation under various physiological states of patients.

The sample data is obtained during separate measurement cycle of $1h$ duration at which the parallel measurement data from the investigated measurement device and the standard measurement device are registered. In this way, up to 180 000 parallel measurement points are obtained at each measurement cycle. For the data obtained, the Student's distribution test statistic for paired or correlated samples [1] with the significance level 5% is applied to evaluate a coincidence of the measurement results. Therefore, for each measurement cycle a decision is stated (accept or reject the hypothesis on the coincidence of results).

The consistency of the decisions is to be tested for repeated measurement cycles under various physiological states of patients. The number of measurement cycles is calculated using a general formula for the significance test of a single proportion [2]:

$$n > \frac{\left[u\sqrt{\pi(1-\pi)} + v\sqrt{\pi_0(1-\pi_0)}\right]^2}{(\pi-\pi_0)^2}, \qquad (1)$$

where

n - required minimum size of measurement cycles;

π - proportion of interest;

π_0 - null hypothesis proportion;

u - one-sided percentage point of the normal distribution corresponding to 100% - $power$;

v - percentage of the normal distribution corresponding to the required (two-sided) significance level.

For our investigations we have introduced the following values of the formula (1) parameters: the proportion of interest $\pi = 0.95$; the null hypothesis (measurement results by the investigated and standard methods coincide) proportion $\pi_0 = 1$; the power value for demonstrating the significant difference between results of measurement cycles is accepted $power = 95\%$, which corresponds $u = 1.645$; the significance level is accepted 5%, which corresponds $v = 1.96$.

With the above parameter values, the following value of required measurement cycles is calculated:

$$n > \frac{\left[1.645\sqrt{0.95(1-0.95)} + 1.96\sqrt{1(1-1)}\right]^2}{(0.95-1)^2} = 52 \qquad (2)$$

Under specific experimental conditions, a separate patient can be tested 2 times per day during 5 days. Therefore, the maximum 10 measurement cycles can be obtained from one patient, and the minimum number of patients to obtain the required statistics of samples is

$$whole\ number\left(\frac{52}{10}\right) = 6 \text{ (patients).} \qquad (3)$$

The real number of measurement cycles obtained from one patient, however, can be less than 10 (in practice it vary from 1 to 10), if the physiological state of a patient does not change and the repeated measurement cycles are not informative. The criteria of change are: the state of blood flow autoregulation is changed or CPP, ABP or ICP values are significantly changed, or B waves became active.

Taking into account the above circumstances, we have increased the calculated value to 10 patients in order to ensure the required statistics of samples under unfavourable experimental conditions.

Specification of the statistical power analysis

As it has been demonstrated by calculation, presented earlier, the statistics of informative number of measurement cycles $N > 52$ provides a required power of conclusions. The number of subjects to obtain the required statistics of samples is determined 10.
Assuming idealistic case, if the maximum number of informative samples (10) is obtained from each patient, the whole number of samples available for statistical analysis is $10 \times 10 = 100$. This number significantly exceeds a required minimum value ($N > 52$).
Thus, experimental data available from 10 patients provide a significant reserve for obtaining a required statistics of informative samples, taking into account that the real number of informative samples obtained from separate patient can be less then 10.
A more exact statistical calculation of required number of subjects can not be performed, as there is no *a priori* information about statistical distribution of the numbers of informative samples obtained from one patient.
Referring on the above reasoning we have determined the number 10 of subjects as a definitive number for obtaining the required statistics of samples.
Under extremely unfavorable conditions of experimental tests, if the minimum number ($N > 52$) of informative samples were not obtained from 10 patients, the experimental research will be extended by introducing extra patients until the required number of informative samples is obtained.

The data analysis plan

1. *Processing of measurement cycles experimental data in order to evaluate for each measurement cycle a coincidence of measurement data from the investigated measurement device and the standard measurement device.*

Calculation is based on the paired data of parallel measurements

$$\left(x_{inv}\right)_i,\ \left(x_{st}\right)_i,\ i=1,\ \ldots,\ n, \tag{4}$$

where $\left(x_{inv}\right)_i$ is measured value by the investigated device; $\left(x_{st}\right)_i$ is measured value by the standard device; i is index of measurement point; and n is a number of measurement points (up to $180\ 000$).

For each measurement point a difference is calculated:

$$D_i = \left(x_{inv}\right)_i - \left(x_{st}\right)_i,\quad i=1,\ \ldots,\ n. \tag{5}$$

Testing the hypothesis on equality of population means is based on calculated value of the test statistic [1]:

$$T = \frac{m_D - 0}{\frac{s}{\sqrt{n}}}, \tag{6}$$

which is distributed as Student's t with $n-1$ degrees of freedom.

Parameters m_D (mean) and s (standard deviation) are calculated using formulas:

$$m_D = \frac{1}{n}\sum_{i=1}^{n} D_i, \tag{7}$$

$$s = \sqrt{\frac{1}{n-1}\sum_{i=1}^{n}\left(D_i - m_D\right)^2}. \tag{8}$$

The calculated value T is compared with the critical value t, obtained from the statistical table of t-distribution values for the $n-1$ degrees of freedom and 5% significance level.

If $|T| < t$, the hypothesis on equality of population means is accepted, otherwise the hypothesis is rejected.

In this way, for each measurement cycle a decision is stated: accept or reject the hypothesis on the coincidence of results.

2. *Statistical analysis of results of the informative measurement cycle tests in order to evaluate a coincidence of measurement results for the entire population of samples.*

For the investigated number N of informative samples ($N > 52$), a proportion π_{N+} of samples (N_+) with the positive decision on the coincidence of measurement results is calculated:

$$\pi_{N+} = N_+ / N. \tag{9}$$

The calculated value π_{n+} is compared with the proportion of interest $\pi = 0.95$.

If $\pi_{N+} > \pi$, the hypothesis on the coincidence of measurement results is accepted. Otherwise the hypothesis is rejected.

References:

[1] N.L. Johnson, F.C. Leone. Statistics and Experimental Design in Engineering and Physical Sciences. John Wiley & Sons, 1977.
[2] B.R. Kirkwood. Essentials of Medical Statistics. Blackwell Science Ltd, 1988.

5. Protocol design

The steps that will be taken for each procedure to be performed on each subject are as follows:
- head set positioning,
- evaluation and adjustment of ultrasound signals,
- monitoring trial #1,
- monitoring trial #2,
- head set removal,
- monitoring data processing and storing.

Head Set Positioning and Calibration

Head Set Positioning

The head set will be positioned on the head for transintracranial time-of-flight (TITF) data collection from Vittamed Noninvasive Neurodiagnostic System.

The head set will be positioned on the head symmetrically. The ear supports, a support on the bridge of the nose, upper and back supports will be tightened so that head frame is stable on the head and unable to move. A small individually made plastic cushion will be put on the bridge of nose because the form of the bridge is individual to each subject and will improve their comfort. The posterior arc of the frame can be removed.

The adjustment screen of the software will be turned on. Using the on-line analysis software, the ultrasound probes will be optimally placed in the head frame with coupling gel applied.

Evaluation and adjustment of ultrasound signals

1. The correct position of the ultrasound probes will be established either upon the MRI scan data (if available) or upon the anatomical properties of the subjects' head. The position of the ultrasound probes will always be controlled by the signal software.
2. If the place is inappropriate, the probes can be moved upward or downward, backward or forward to any position.
3. If the acoustic contact will be too low, more gel can be added.
4. Once the optimal position is obtained, the ultrasound probes will be tightened and fixed.

Patient Protocol

Measurement Trials will be taken from each patient at least twice per day to fit in with times which are convenient for the ICU nurses.

Measurement Trial No. 1

The Measurement Trial No. 1 is the simultaneous recording of invasive ICP, invasive ABP and noninvasive transintracranial time-of-flight data. The data will include pulse waves, slow waves (Lundberg's B waves) and the mean value (ICP, ABP and time-of-flight) trends. The duration of measurement trials will be 1 hour or more. The noninvasive monitoring procedures will have no

negative impact on the subject's clinical management and no additional risks may be created for the subject regarding impact on the expected care, safety and well being and standard medical recovery period. The benefit for subject from noninvasive monitoring sessions is explained in item 6 of this protocol.

The number of trials will depend on the pathophysiological state of the patient under trial. The trial will be repeated only in the cases when the ICP or ABP will be significantly changed or if B waves activity will occur or the cerebral blood flow autoregulation state will be significantly changed. We intend to repeat the trials every day during the patient treatment in the ICU but not longer than 5 days because the invasive ICP probe needs to be removed after that.

A pro-forma data collection sheet will be completed for each measurement trial (see Appendix A).

Measurement Trial No. 2

The Measurement Trial No. 2 is the simultaneous recording of invasive ICP, invasive ABP and noninvasive two depth TCD data from the coma patient eye arteries intracranial and extracranial segments. The duration of such the data recordings will be 2 - 3 minutes.

We intend to repeat trial No. 2 twice a day during the patient treatment in the ICU. We will repeat trial No. 2 only in the cases when patient's ICP is significantly changed. If ICP is stable, trial No. 2 will not be repeated.

A pro-forma data collection sheet will be completed for each measurement trial (see Appendix B).

6. Risk / benefits Assessment:

The brain injured patients at risk of raised intracranial pressure will be monitored applying existing standard invasive monitoring technologies following Guidelines for the Management of Severe Head Injury, 1995, American Association of Neurological Surgeons. Acoustic output of Vittamed Noninvasive Neurodiagnostic System is below pre-amendments fetal level (below the level of acoustic field emission which is used in commercially available ultrasonic fetal imaging devices) and no safety question for patient occur.

If patient's cerebral blood flow autoregulation is impaired, use of arterial pressors to raise systemic arterial pressure, as a means of increasing of abnormally low cerebral perfusion pressure, is not indicated. The time moment of the beginning of the impaired autoregulation state can not be detected if the cerebral blood flow autoregulation state is not monitored continuously. Ultrasonic noninvasive monitoring technology is the only existing technology for reliable continuous monitoring of the cerebral blood flow autoregulation state during monitoring sessions.

The patient will directly benefit from the more often follow-up examinations and additional diagnostic information evaluated by neurosurgeons and intensive care physicians participating in the study. We intend to examine patients enrolled in the study to make better targeted treatment decisions four times more often comparing with the standard treatment recommended in Guidelines for the Management of Severe Head Injury, 1995, American Association of Neurological Surgeons.

Additional diagnostic information will be obtained from noninvasive continuous monitoring of the cerebral blood flow autoregulation state using noninvasive slow parenchymal blood volume wave data correlated with the systemic arterial blood pressure slow wave data. Direct benefit will be obtained due to decreased risks of undetected brain secondary insults as a result of impaired autoregulation and every indication obtained from the noninvasive monitor will call for prompt additional standard diagnostic testing and treatment. The noninvasive data is obtained from the acoustic path which is the space integral between ultrasonic transducers and the ultrasound beam diameter. Thus, comparing with invasive local space fibber optic intracranial pressure transducers, we have a more accurate evaluation of the causes of intracranial pressure changes - blood volume changes inside the parenchyma.

In the case of local severe head injury and brain swelling intracranial pressure gradients between cerebral hemispheres can occur. In that case, an invasive unilateral ICP monitor is unable to detect the intracranial pressure gradients. The benefit obtained from the transcranial Doppler measurements of the eye arteries blood flows will be the ability to detect noninvasively such intracranial pressure gradients. Noninvasive measurements through the eyes will be performed through both eyes of the subject under study. The additional standard diagnostic procedures (MRI, CT) will be performed in cases where we find the appearance of the intracranial pressure gradients. This additional standard diagnosing and treatment decisions will be of benefit to the patient.

When blood flow in the eye artery is measured an external low pressure will be added to the eye. The maximal value of the added pressure will be less than 30 mmHg because we intend to study only a limited range of ICP values below and above the critical ICP level 20.0 ... 25.0 mmHg. This level of pressure is equivalent to a change in atmospheric pressure within 300 m altitude or change in water pressure at the depth 0.5 m. No additional risks or research related injury for the subject under study will be caused by using such an external pressure to the eye and by using of standard ultrasonic Doppler device.

No additional risks for subject under study will be caused by using the noninvasive device during the hour period that the device will be in place during the two times a day and no limitations for the subjects mobility will be caused by using the noninvasive device.

7. Reporting of Serious and Unexpected Adverse Events

Adverse experiences that are both serious and unexpected will be immediately reported by telephone to the USAMRMC Office of Regulatory Compliance and Quality (301-619-2165) (non-duty hours call 301-619-2165 and send information by facsimile to 301-619-7803). A written report will follow the initial telephone call within 3 working days. Address the written report to the U.S. Army Medical Research and Materiel Command, ATTN: MCMR-RCQ, 504 Scott Street, Fort Detrick, Maryland 21702-5012.

An adverse event temporally related to participation in the study should be documented whether or not considered to be related to the test article. This definition includes intercurrent illnesses and injuries, and exacerbation of preexisting conditions. Include the following in all IND safety reports: Subject identification number and initials; associate investigator's name and name of MTF; subject's date of birth, gender, and ethnicity; test article and dates of administration; signs/symptoms and severity; date of onset; date of resolution or death; relationship to the study drug; action taken; concomitant medication(s) including dose, route and duration of treatment, and date of last dose.

8. Medical Monitor

A medical monitor is assigned to this study. The name of the medical monitor is Bronius Spakauskas, MD. The *Curriculum vitae* of the medical monitor Bronius Spakauskas is provided. This individual is a qualified physician, other than the Responsible Investigator, not associated with this particular protocol, able to provide medical care to research subjects for conditions that may arise during the conduct of the study, and who will monitor the subjects during the conduct of the study. The medical monitor is required to review all serious and unexpected adverse events (per ICH definitions) associated with the protocol and provide an unbiased written report of the event within 10 calendar days of the initial report. At a minimum, the medical monitor should comment on the outcomes of the adverse event (AE) and relationship of the AE to the test article. The medical monitor should also indicate whether he concurs with the details of the report provided by the study investigator.

9. Disposition of Data

The data will be stored in Vitta Corporation (Bethel, CT, USA) for 5 years after the completing of the research. The data analysis will be based on the hypotheses statistical testing methodology (e.g., applying $\chi 2$ criterion) and statistical calculation of monitored data uncertainty methodology.

10. Review of research records

It should be noted that representatives of the US Army Medical Research and Materiel Command are eligible to review research records as a part of their responsibility to protect human subjects in research.

11. Roles and Responsibilities of Study Personnel

V. Deltuva, MD and A. Matukevicius, MD will implant the standard invasive transducers and will assist the studies, will be responsible for acquisition of the Consent Form,
G. Daubaris, DSc. will perform the monitors operating and monitoring data collection and storing, documentation and maintenance of the study records and subject data, maintenance and quality assurance checks of the device,
R. Tarasevicius, Dr. will perform the treatment of ICU coma patients as an intensive care unit's physician, will be responsible for the education of the ICU staff.

12. Recruitment and Inform Consent Process

Recruitment process will involve discussion with the family member of the comatose patient who could be the subject of investigations and encouragement to ask all possible questions. No additional recruitment materials will be used. Only the consent to participate in research form will be used during the discussion with the family member of the potential subject of investigation.

Responsible for the consent process will be the member of clinical study personnel Dr. A. Matukevicius who will be on duty at the moment of the appearance of comatose patient in the ICU.

The photographs or videotapes of the subjects will not be produced.

13. Procedure to be followed if a modification of the protocol, consent form or protocol related documents becomes necessary

Any changes in the protocol must first be approved by the local Ethics Committee and the Department of the Army Human Subjects Research Review Board (HSRRB) before implementation of the modifications. The nature of the modification will determine the type and level of review.

14. Responsibilities of the Responsible Investigator to the Surgeon General through the USAMRMC, Office of Regulatory Compliance and Quality

14. 1. To promptly report changes or unanticipated problems in a research activity. Normally, changes may not be initiated without TSG approval, except where necessary to eliminate apparent immediate hazards to the human subject or others.
14. 2. To immediately report by telephone (DSN 343-2165 or 301-619-2165) (non-duty hours call 301-619-2165 and send information by facsimile to DSN 343-7803 or 301-619-7803) adverse experiences that are both serious and unexpected.* For those projects involving an Investigational New Drug (IND) application sponsored by TSG, a written report will follow the initial telephone call within 3 working days.
14. 3. To promptly report any change of investigators.
14. 4. To prepare, at a minimum, an annual progress report or final report in accordance with Title 21, Code of Federal Regulations, Part 312.33.
14. 5. To immediately report by telephone (DSN 343-2165 or 301-619-2165) knowledge of a pending compliance inspection by the Food and Drug Administration (FDA) or other outside governmental agency concerning clinical investigation or research. *"Serious adverse experience" means any experience that suggests a significant hazard, contraindication, side effect, or precaution. With respect to human clinical experience, a serious adverse drug experience includes any adverse drug experience that is fatal or life-threatening, is permanently disabling, requires inpatient hospitalization, or is a congenital anomaly, cancer, or overdose. "Unexpected adverse experience" means any adverse experience that is not identified in nature, severity, or frequency in the current investigator brochure; or, if an investigator brochure is not required, that is not identified in nature, severity, or frequency in the risk information described in the general investigational plan or elsewhere in the current application, as amended.

15. Signature of Responsible Investigator

"I have read the foregoing protocol and agree to conduct the study as outlined herein".

Responsible Investigator Arminas Ragauskas, DSc.

Signature:  Date Sept. 05 2009

DEPARTMENT OF THE ARMY
US ARMY MEDICAL RESEARCH AND MATERIEL COMMAND
504 SCOTT STREET
FORT DETRICK, MARYLAND 21702-5012

REPLY TO
ATTENTION OF:

MCMR-RMI-S (70-1y) 18 Apr 03

MEMORANDUM FOR Administrator, Defense Technical Information Center (DTIC-OCA), 8725 John J. Kingman Road, Fort Belvoir, VA 22060-6218

SUBJECT: Request Change in Distribution Statement

1. The U.S. Army Medical Research and Materiel Command has reexamined the need for the limitation assigned to technical reports written for this Command. Request the limited distribution statement for the enclosed accession numbers be changed to "Approved for public release; distribution unlimited." These reports should be released to the National Technical Information Service.

2. Point of contact for this request is Ms. Kristin Morrow at DSN 343-7327 or by e-mail at Kristin.Morrow@det.amedd.army.mil.

FOR THE COMMANDER:

Encl

Phyllis Rinehart
PHYLLIS M. RINEHART
Deputy Chief of Staff for
Information Management

ADB285846
ADB255323
ADB246514
ADB233740
ADB286395
ADB275662
ADB285859
ADB272667
ADB259790

Full